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BULLETIN OF
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CHAIN PROCESSES AND THEIR BIOPHYSICAL APPLICATIONS:

PART I. GENERAL THEORY

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A mathematical theory applicable to the biological effects of radiations as chain processes is developed. The theory may be interpreted substantially as a "hit theory" involving the concepts of "sensitive volume" or "target area". The variability of the sensitivity of the organism to the radiation and its capacity of recovery between single hits is taken into account. It is shown that in a continuous irradiation of a biological aggregate in which the effect of each single hit cannot be observed, recovery and variation of sensitivity are formally equivalent to each other so that a discrimination between these two phenomena is possible only by discontinuous irradiation or by using different radiation intensities. Methods for the calculation of the "number of hits" and for the determination of the kinetics of the processes from "survival curves" or similar experimental data are given. The relation between the recovery and the Bunsen-Roscoe law is discussed. The case in which the injury of the organism is dependent on the destruction of more than one "sensitive volume" is also considered.

1. Introduction. The changes that living organisms undergo when subject to the action of a physical or chemical agent are often successive transformations: the organism, or a part of it, passes successively through various states before a certain condition accessible to a direct experimental observation is reached. A theory of such processes has a twofold objective: (1) to obtain some information about the states which cannot be observed in a direct manner, about their kinetics, their rates and their number; (2) to correlate the observed facts with the structure of the microorganism by determining that part of it which is the first biological cause in the chain of changes that the organism undergoes under the action of the external agent. That part, the *sensitive volume* of the organism (called also, perhaps in a less appropriate manner, its *sensitive area*), is formed, according to present viewpoints, of some heavy molecule or molecules which have a vital biological function and whose decomposition causes some more or less permanent change of the organism, its injury, or death (cf. e.g. Jordan, 1939). Although obviously not all physicochemical agents can be conveniently accounted for by such concept of sensitive volume, the latter seems to be suitable for an interpretation of *biological effects of radiations.*

The usefulness of radiations as therapeutic means, their appropriateness for investigations in various branches of biology, the very large experimental material which is available in these fields, and the hope that someday it may lead to a deeper understanding of the structure of the living matter, create the need of a synthetic theory of these biophysical phenomena.

The present work is developed from the existing mathematical approach in this field based substantially on the concept of a chain process. The paper gives practical means of application of the theory and shows also some of its limitations.

Since in a later part of the paper the theory will be applied to some experimental results on biological effects of radiations, it is convenient to mention here the character and the order of magnitude of the phenomena in this field. The average minimum energy necessary to produce erythema of human skin by ultraviolet light is 1.8×10^5 erg/cm^2 at 2967 Angstrom (Blum, 1944, pp. 1145-1163). This corresponds to 10^{11} quanta per cell, if one assumes an average size of epithelium cell of $400\mu^2$ (cf. Hoerr, 1944, pp. 135-139). Since the passage of a photon into or through the cell can be identified, from a general viewpoint, with a new state of the cell, it is seen that we have to do here with an enormous number of states, which is further multiplied by the fact that the capture of a photon by a cell is only a first step in a chain of transformations consisting of activation of molecules, ionizations, chemical reactions, etc. (cf. e.g. Blum, 1944, pp. 1145-1163; Failla, 1936, pp. 87-122; Fano and Demerec, 1944, pp. 499-512; Lea, Haines, and Coulson, 1936; Noddack, 1933, p. 330). A similar computation could be made also for irradiation by X rays, or to get a closer picture of the process, one could identify the change of a state of the cell with a liberation of an electron in it or with a penetration of a primary or secondary electron into the cell. Theoretical formulae for such total number of electronic tracks in or through a sensitive volume of living matter were given by R. Glocker (1932) in relation to the wave length, the penetrating range of the electron and the size of the sensitive volume. In an irradiation of a sample of ascaris eggs by X rays, A. Zuppinger (1928, p. 755) estimated roughly an average number of 10^8 electrons liberated per cell at the time when one-half of the eggs of the sample were injured. These examples show how large is the number of events involved in an irradiation process. However, a mathematical analysis of experimental data reveals sometimes a single event only; for instance, in many cases of killing bacteria by ultraviolet light or induction of gene mutations by X rays; in other cases the number of events is larger but seldom exceeds an order of magnitude of 50 or 100. This apparent disagree-

ment is explained by the assumption that the sensitive volume is extremely small with respect to the size of the cell, so that the number of events accounting for the final effect is also small.

2. General equations. To make the mathematics more concrete and in view of the applications that will be made in a later part of the paper, the theory will be developed by referring as an example to the biological effects of radiations. Consider a microorganism capable of assuming $n + 1$ states which will be numbered $0, 1, \cdots, n$. We will limit ourselves to the case in which an organism in a state i may pass directly only either to the state $i + 1$ (*"direct process"*) or to the state $i - 1$ (*"reverse process"*). In the irradiation of microorganisms the number of states is often interpreted as the number of collisions of photons with the sensitive volume, although there are possibilities of a much broader interpretation. In any case, the "direct process" is in this field very often a *process of injury* of the organism and the "reverse process", a *process of recovery*. The state 0 represents then living organisms in normal conditions and the state n may represent dead organisms. Consider a homogeneous aggregate of N microorganisms and call $NY_i(t)$ the number of those microorganisms which are in the state i at the time t. If we call $ND_i(t)$ the time rate with which the microorganisms pass from the state i—1 into the state i (direct or injury process) and $NR_i(t)$ the time rate with which the microorganisms pass from the state i+1 into the state i (reverse or recovery process), then

$$dY_i/dt = D_i - D_{i+1} + R_i - R_{i-1}. \tag{1}$$

The simplest intuitive assumption concerning the D_i's is

$$D_i = k_i Y_{i-1}, \tag{2}$$

where k_i depends on the intensity of radiation and on the *sensibility of the organism* in the state i—1 to a given radiation. Consequently, the k_i's depend on the *probability of collision* between a photon and the sensitive volume.

As to the rates of recovery, we will assume, following an idea of W. Swann (Swann and Del Rosario, 1931),

$$R_i = g_i Y_{i+1}, \tag{3}$$

where g_i represents the *intensity of recovery* of the microorganisms from the state i+1 to the state i, in a way similar as k_i in equation (2) represents the *intensity of injury* of the microorganisms in the state i—1. The process of recovery does not need to be necessarily of a biological character because it occurs also in a variety of purely

physical phenomena; for instance, in the action of light on a photographic emulsion it is known as "fading of activated emulsion grains" (cf. e.g. Silberstein, 1939; Long, Germann, and Blair, 1935).

Consider the case in which at the beginning of irradiation ($t = 0$) all microorganisms are in the state 0. Then

$$Y_0(0) = 1\,, \qquad Y_i(0) = 0 \text{ for } i > 0\,. \tag{4}$$

Very often we may look upon the state n as representing some effect of radiation; in many cases that state corresponds to the only observable degree of injury, although in some cases intermediate states (for instance, the degree of skin erythema) may be also discerned with sufficient accuracy for measurements or counting. The process of recovery, as represented by equation (3), does not involve the actual possibility of recovery from any state to all the preceding ones. If, for instance, a certain $g_{j-1} = 0$, such possibility is precluded, and one could say that there is some kind of barrier between the states j—1 and j which the organisms cannot pass by recovering (see Sec. 6).

Besides the idea of W. Swann, which is generalized in equation (3), other methods of taking into account the recovery are known in the literature. For instance, J. Reboul (1939) treats the recovery in a global manner as an exponential relationship between the number of totally recovered microorganisms and the time. Such approach does not take into account the different states or degrees of recovery. Other authors consider the radiation energy absorbed by the organisms and converted by them into a change of their state as decreasing exponentially with the time by a process of recovery (Williams, 1934; Taylor and Pohle, 1938, p. 160; Holthusen and Braun, 1933, pp. 204-205; Lea, 1938, pp. 493-494, 555-558; Lea, 1941, p. 609).

Equation (1) involves the basic assumption that the process is sufficiently intense so that the representation of the time rate by the derivative dY_i/dt is sufficiently accurate. Consequently, considering, for instance, the state n, the theory appears less accurate for small values of t, because of the conditions (4).

The use of equation (3) involves the assumption that the time necessary for an organism to recover from a state to the preceding one is very short with respect to the total duration of radiation. A method taking into account the duration of recovery of each single organism will be discussed in a later part of the paper.

We have the obvious relations:

$$\left.\begin{aligned} &D_0 = k_0 = 0; \qquad D_i > 0\,,\ k_i > 0 \text{ for } 1 \leqq i \leqq n\,, \\ &D_{n+1} \geqq 0\,, \quad k_{n+1} \geqq 0\,, \\ &R_i \geqq 0\,, \quad g_i \geqq 0 \text{ for } 0 \leqq i \leqq n-1\,, \\ &R_n = g_n = 0 \end{aligned}\right\}\,. \tag{5}$$

The last of these relations involves the assumption which we make throughout the paper that *a recovery is impossible into the* n-*th state.* Usually this is the *final state* of the process, and in such case we have

$$D_{n+1} = k_{n+1} = R_n = g_n = 0\,, \tag{6}$$

The conditions $k_{n+1} = g_n = 0$ may be interpreted also on the basis of equations (1) to (5), from which

$$d \sum_{i=0}^{i=n} Y_i/dt = -k_{n+1}\, Y_n + g_n\, Y_{n+1} = 0$$

may be easily derived, so that by equation (4), $\sum_{i=0}^{i=n} Y_i = 1$, i.e., the total number of microorganisms in the states $0\,,\ 1\,,\ \cdots\,,\ n$ is always the same at any time t. In other words, the states $0,\ 1,\ \cdots\,,\ n$ involve a *closed system of transitions.*

If no recovery is possible from the final state, then also

$$R_{n-1} = g_{n-1} = 0\,. \tag{7}$$

For the sake of brevity, all equations will be written for a general state i and it is agreed throughout the paper that all quantities with negative subscripts are zero by definition.

The intensities k_i and g_i will be assumed constant for each state i. Their possible dependence on time, as it occurs, for instance, during the mitotic division of a cell (cf. Henshaw, 1944; Pack and Quimby, 1932) or in relation to its age (cf. Henshaw and Henshaw, 1933; Rentschler, Nagy, and Mouromseff, 1941; Sax and Swanson, 1941), may be taken into account by putting k_i and g_i in the form of a prodduct of the type

$$k_i = \phi(i) f(t), \qquad g_i = \psi(i) f(t), \tag{8}$$

and taking $\int f(t)\,dt$ as the time variable instead of t (cf. Opatowski, 1942). Equations (8) involve the assumption that either one of the two processes, injury or recovery, is not taking place, or that the ratio of the intensities of the two processes does not change with the time.

The fact that transitions between two consecutive states are considered as the only possible in the direct process is a consequence of the assumption that the physico-chemical agent (e.g. the radiation quanta) as well as the biological aggregate are both homogeneous, that there is only one sensitive volume in each microorganism (cf. Sec. 7), and that the probability of a simultaneous action of two physico-chemical entities (e.g. quanta) in one sensitive volume is negligible. The consideration of the same states during recovery may be

looked upon at least as an approximation. For instance, the photochemical processes of vision as they occur in the rods of human retina offer an example of such approximation; there are three states here which are determined by the products of a decomposition of the original components of the rods, the rhodopsin; the recovery occurs between the second and the first state and directly between the third and the first, but the latter is of negligible amount (Moon and Spencer, 1945). The possibility of obtaining biologically homogeneous aggregates through appropriate subcultures has been shown in the bacteriological field by H. C. Rentschler, *et al* (Rentschler, Nagy, and Mouromseff, 1941; Rentschler and Nagy, 1942).

3. Solution of the equations. A convenient method to determine the functions $Y_i(t)$ from equations (1) to (4) is to use the Laplace transformation; that is, to associate with each function $Y_i(t)$ a function $y_i(s)$ defined by

$$y_i(s) = \int_0^\infty e^{-st}\, Y_i(t)\, dt\,. \tag{9}$$

Then by known theorems (Doetsch, 1937, p. 153; Churchill, 1944, p. 6),

$$\int_0^\infty e^{-st}(dY_i/dt)\, dt = sy_i(s) - Y_i(0),$$

so that multiplying both sides of equations (1) by $e^{-st}dt$ and integrating between 0 and ∞, we obtain the following linear system of equations in y_i's:

$$\left.\begin{aligned} (s + 2I_0)\, y_0 - g_0 y_1 &= 1\,, \\ -k_i y_{i-1} + (s + 2I_i)\, y_i - g_i y_{i+1} &= 0 \text{ for } i \geqq 1 \end{aligned}\right\}, \tag{10}$$

where $2I_i = k_{i+1} + g_{i-1}$, so that I_i is the *arithmetic average of the intensities with which the microorganisms abandon the state* i *by direct and reverse process.*

The solutions of the system (10) are

$$y_i = P_i D(i + 1\,, n)/D(0\,, n), \tag{11}$$

where

$$P_0 = 1\,, P_i = k_1 k_2 \cdots k_i \text{ for } i \geqq 1\,, \tag{12}$$

$D(n + 1\,, n) = 1$, and any other $D(i\,, n)$ is a determinant of order $n - i + 1$ whose only elements different from zero are those of the principal diagonal and of the two contiguous parallel lines, the "upper" and the "lower" diagonals.

$$D(i,n)=\begin{vmatrix} s+2I_i, & g_i, & 0, & 0, & \cdots \\ k_{i+1}, & s+2I_{i+1}, & g_{i+1} & 0, & \cdots \\ 0, & k_{i+2}, & s+2I_{i+2}, & g_{i+2}, & \cdots \\ \cdots & \cdots & \cdots & \cdots & \cdots \\ 0, & \cdots & k_{n-1}, & s+2I_{n-1}, & g_{n-1} \\ 0, & \cdots & 0, & k_n, & s+2I_n. \end{vmatrix} \tag{13}$$

Determinants of this type are called continuants because of their connection with continuous fractions (Muir and Metzler, 1930, pp. 526, 560, 561; Hellinger and Wall, 1943); they occur also in the theory of optical instruments (Rosin and Clark, 1941). An alternative form of $D(i,n)$ which we need is obtained from expression (13) by changing the sign of each g and of each k in the upper and lower diagonals. This does not change the value of the determinant by known theorems (Muir and Metzler, 1930, p. 25). The proof of equation (11) is obtained by applying Cramer's rule. In fact, the determinant of the coefficients of the y_i's in the system (10) is $D(0,n)$. The determinant Δ_i obtained from $D(0,n)$ by changing its $(i+1)$-st column into $1, 0 \cdots 0$ has the following character: if one draws a vertical line between the $(i+1)$-st and the $(i+2)$-nd columns and a horizontal line between the $(i+1)$-st and the $(i+2)$-nd rows, one obtains four rectangular arrays, such that the elements of the left bottom array are all zero. Such a determinant equals the product of the determinants formed by the left top and the right bottom arrays. The latter is $D(i+1,n)$ and the former is easily seen to be P_i (Muir and Metzler, 1930, pp. 103, 57), so that

$$\Delta_i = P_i D(i+1,n),$$

which proves equation (11).

We need an expansion of $D(i,n)$ as a polynomial of s. Call $D_0(i,n)$ the value of $D(i,n)$ for $s=0$, and $M_j(i,n)$ a principal minor of order j of $D_0(i,n)$; that is, a minor whose principal diagonal is a part of the principal diagonal of $D_0(i,n)$, then (Muir and Metzler, 1930, p. 72)

$$D(i+1,n) = s^{n-i}\left[1+\sum_{j=1}^{n-i} s^{-j}\,\Sigma_M M_j(i+1,n)\right], \tag{14}$$

where Σ_M stands for the sum of all the principal minors M_j of $D_0(i+1,n)$. In this way, each coefficient of s^{-j} in equation (14) is a sum of $\binom{n-i}{j}$ determinants of j-th order with the obvious relation

$$M_{n-i}(i+1,n) = D_0(i+1,n).$$

For instance, for $D(0,n)$, i.e. for $i+1=0$, we have

$$\left.\begin{aligned}
\Sigma_M M_1(0,n) &= 2\sum_{r=0}^{r=n} I_r, \\
\Sigma_M M_2(0,n) &= \sum_{\substack{r,s=0 \\ r<s}}^{r,s=n} \begin{vmatrix} 2I_r, & g_r \\ k_s, & 2I_s \end{vmatrix}, \\
\Sigma_M M_3(0,n) &= \sum_{\substack{r,s,t=0 \\ r<s<t}}^{r,s,t=n} \begin{vmatrix} 2I_r, & g_r, & 0 \\ k_s, & 2I_s, & g_s \\ 0, & k_t, & 2I_t \end{vmatrix}, \text{ etc.}
\end{aligned}\right\} . \qquad (15)$$

From expressions (11) and (14) the expansion of $y_i(s)$ in power series of $1/s$ may be calculated. In particular, for the n-th state we have

$$\left.\begin{aligned} y_n(s) = P_n/D(0,n) = P_n/\{s^{n+1}[1 + \Sigma_M M_1(0,n)s^{-1} + \\ \Sigma_M M_2(0,n)s^{-2} + \cdots + D_0(0,n)s^{-n-1}]\} \end{aligned}\right\} , \qquad (16)$$

$$y_n(s) = P_n s^{-n-1}(1 + \sum_{j=1}^{\infty} a_{n,j}\, s^{-j}) , \qquad (17)$$

where the a's are obtained in terms of the Σ_M's by the ordinary rules of division of power series, so that

$$\left.\begin{aligned} a_{n,1} = -\Sigma_1; \qquad a_{n,2} = \Sigma_1^2 - \Sigma_2; \\ a_{n,3} = -\Sigma_1^3 + 2\Sigma_1\Sigma_2 - \Sigma_3; \text{ etc.} \end{aligned}\right\} , \qquad (18)$$

where for brevity $\Sigma_j = \Sigma_M M_j(0,n)$. By a known formula of the Laplace transform (Doetsch, 1937, p. 62; Widder, 1941, p. 94), we finally have from equation (17)

$$Y_n(t) = P_n t^n \left[(n!)^{-1} + \sum_{j=1}^{\infty} a_{n,j}\, t^j/(n+j)! \right] , \qquad (19)$$

which is obviously convergent for any finite t, because by equations (1), (2), and (3), $Y_n(t)$ is a sum of exponential functions of t multiplied by polynomials of t. By equation (12), P_n does not depend on the g_i's, therefore in a sufficiently short experimentation (t small), the recovery process does not affect the function $Y_n(t)$.

Some conclusions of a general character may be derived from equation (19): In the field of radiations, the intensities of injury k_i must be assumed, at least in a first approximation, as directly proportional to the radiation energy per unit time, i.e. to radiation intensity J:

$$k_i = J\,\kappa_i . \qquad (20)$$

The reverse intensities g_i, which represent the recovery process, may

be assumed in a first approximation as independent, or perhaps inversely proportional to J since they may involve a physiological reaction of the whole organism. The well-known fact that tumor cells are not damaged by low radiation intensities (cf. Wood, 1944, pp. 88-89) but are destroyed at high intensities can be explained only by assuming that higher intensities of radiation involve smaller intensities of recovery g_i. The assumption of inverse proportionality between g_i and J would involve an infinite intensity of recovery at zero intensity of radiation, which in itself cannot be considered as a contradiction of experimental facts.

Now from equations (15) and (18) it is seen that $a_{n,j}$ is a homogeneous function of degree j in the k_i's and g_i's. Therefore, if there is no recovery ($g_i = 0$), the coefficient of t^j in expansion (19) is of degree j also in J, by equation (20). Consequently, the effect of radiation, as represented by $Y_n(t)$, does not change if the intensity and the time of radiation change according to the condition $Jt = \text{const}$. We obtain in this way an interpretation from the viewpoint of the chain processes of the so-called *reciprocity law* asserting that a radiation effect depends on the total energy and not on its time distribution (Bunsen and Roscoe, 1862). The reverse intensities g_i take into account what is known in physico-chemistry as the failure of this law or the *time effect*; in biological fields they represent the recovery process on which the radiation-therapeutic concepts of *fractional* and *cumulative dosis* are based (cf. e.g. Taylor and Pohle, 1938, pp. 159-167; Holthusen and Braun, 1933, pp. 198-207).

4. Numerical methods: First approximation methods. As has been mentioned, the most common case of application is the one in which of the $n+1$ states, 0 and n are the only observable states; expansion (19) gives then a possibility of obtaining some information as to the laws governing the process from experimental data. In fact, from equation (19) we have

$$\log Y_n = \log P_n - \log n! + n \log t + \log\left[1 + \sum_{j=1}^{\infty} n!\, a_{n,j}\, t^j/(n+j)!\right]. \quad (21)$$

For sufficiently small values of t, the sum $\sum$ in $[\cdots]$ is negligible with respect to 1, so that the right hand side of equation (21) reduces to its first three terms, and $\log Y_n$ plotted against $\log t$ is a straight line whose slope equals the *number of states n* and the intercept on the ordinate axis gives the *geometric average of the intensities of injury* $P_n^{1/n}$. If larger values of t are considered and consequently terms of second order in $[\cdots]$ are taken into account, the sum

$$a_{n,1} = \sum_{r=0}^{r=n} k_{r+1} + g_{r-1}, \tag{22}$$

may also be obtained from experimental values of $Y_n(t)$. If the n-th state is the final one ($k_{n+1} = 0$), we may calculate approximately the *arithmetic average* G *of the intensities of recovery* g_0, g_1, $\cdots$ g_{n-1} from equation (22),

$$a_{n,1} \approx nP_n^{1/n} + nG, \tag{23}$$

where the arithmetic average of the k_i's is taken approximately equal to its geometric average. Formula (23) is exact if $k_1 = k_2 = \cdots = k_n$. In all other cases it gives a value of G which is larger than the actual one because the geometric average is smaller than the arithmetic average (Hardy, Littlewood, and Pólya, 1934, pp. 17-18). If the n-th state is the final one from which no recovery is possible ($k_{n+1} = g_{n-1} = 0$), then the above formula should be replaced by

$$a_{n,1} \approx nP_n^{1/n} + nG - G, \tag{24}$$

where G is now the arithmetic average of g_0, g_1, $\cdots$ g_{n-2}.

The *number of states* n, which is sometimes interpreted as a number of hits with photons, may be calculated also by means of the following formula, easily obtainable from equation (21):

$$n = \lim_{t \to 0} [td \log_e Y_n(t)/dt]. \tag{25}$$

The use of formula (25) requires an accurate knowledge of Y_n for small values of t, which experimentally is not easy to achieve for low radiation intensities J. However, since n by its physical meaning is independent of J, a sufficient degree of accuracy may be obtained if curves $Y_n(t)$ are known for various values of J.

5. Formal equivalence between processes with and without recovery. We will show in this section that a chain process (p) with recovery $(g_i \neq 0)$ between the states 0, 1, $\cdots$, n, of which 0 and n are the only observable states, is formally equivalent to a process $(\bar{p})$ without recovery $(g_i = 0)$ between the same number of states with appropriate intensities of injury $\bar{k}_i$. As to the process (p), we assume first that its n-*th state is final* ($k_{n+1} = 0$), and that a *recovery is impossible from that state* ($g_{n-1} = 0$), so that $I_n = 0$. We will see that the process $(\bar{p})$ has also n as its final state, so that $\bar{k}_{n+1} = 0$.

Call $Y_n(t; k_i, g_i)$ and $Y_n(t; \bar{k}_i, 0)$ the functions representing the n-th state of the processes (p) and $(\bar{p})$ respectively. The proof of the above stated "equivalence theorem" consists in showing that

for any set of values $\{k_i, g_i\}$, satisfying the conditions (5) to (7), there exists a set of n real positive numbers $\bar{k}_i$ such that identically

$$Y_n(t; k_i, g_i) = Y_n(t; \bar{k}_i, 0). \tag{26}$$

Instead of proving the relation (26), it is more convenient to prove its Laplace transform, i.e.,

$$y_n(s; k_i, g_i) = y_n(s; \bar{k}_i, 0), \tag{27}$$

or the following relations:

$$k_1 k_2 \cdots k_n = \bar{k}_1 \bar{k}_2 \cdots \bar{k}_n, \tag{28}$$

$$D(0, n; k_i, g_i) = D(0, n; \bar{k}_i, 0), \tag{29}$$

which by equations (11) and (12) imply equation (27). The symbol $D(0, n)$ of equations (11) and (13) has been here replaced by the more explicit ones of condition (29), although for brevity $D(0, j)$ will be also used for $D(0, j; k_i, g_i)$. Since in the determinant expression of $D(0, n; \bar{k}_i, 0)$ in the form of (13) all elements above the main diagonal are zero, it is easy to see that, if the theorem is true,

$$D(0, n; \bar{k}_i, 0) = s(s + \bar{k}_1)(s + \bar{k}_2) \cdots (s + \bar{k}_n).$$

Consequently, in order to show that there exists a set of n real positive numbers $\bar{k}_i$ satisfying the condition (29), it is sufficient to show that the roots of $D(0, n, k_i, g_i)/s = 0$, i.e. of (cf. relation (13)

$$D(0, n-1) = 0, \tag{30}$$

which is an equation of n-th degree in s [cf. relation (16)], are all real and negative. Then, these n roots taken with a changed sign are the values of the $\bar{k}_1, \cdots, \bar{k}_n$, because, as it will be shown, they fulfill also the condition (28).

(*a*). *The roots are all real.* The determinant $D(0, n-1)$ may be represented by the symbol $||a_{r,c}||$, where

$$a_{i,i} = s + 2I_i, \qquad a_{i,i+1} = g_i, \quad a_{i,i-1} = k_i$$

for $i = 0, 1, \cdots, n-1$, all other a's being zero. The reality of the roots is proved by changing $||a_{r,c}||$ into a secular determinant $||b_{r,c}||$. To do this, multiply each i-th row and divide each i-th column of $||a_{r,c}||$ by a number x_i, which will be now determined in a suitable manner. The new determinant $||b_{r,c}||$, whose value is obviously equal to $||a_{r,c}||$, is also a continuant with its main diagonal the same as that of the original determinant,

$$b_{i,i} = a_{i,i} = s + 2I_i ,$$

and the upper and lower diagonals respectively,

$$\left.\begin{aligned} b_{i,i+1} &= a_{i,i+1}\, x_i/x_{i+1} = g_i x_i/x_{i+1} , \\ b_{i,i-1} &= a_{i,i-1}\, x_i/x_{i-1} = k_i x_i/x_{i-1} \end{aligned}\right\} . \tag{31}$$

Now, if we choose x_i in such a manner that $b_{i,i+1} = b_{i+1,i}$, then $||b_{r,c}||$ is a secular determinant. Such a choice is possible by taking x_i according to the relation easily obtainable from equations (31),

$$x_{i+1} = (g_i/k_{i+1})^{1/2}\, x_i ,$$

which determines all x_i's by choosing e.g. $x_0 = 1$. In this way, the secular form of $||b_{r,c}||$ and the reality of the roots in question is proven. It may be noted that in the new determinant

$$b_{i,i+1} = b_{i+1,i} = (g_i\, k_{i+1})^{1/2}$$

has a direct meaning because it represents the *geometric average of the intensities of the processes occurring between the states* i *and* i + 1.

(*b*). *The roots are all negative.* We prove this in the following manner: We show that all the principal minors of $D_0(0\,,\ n-1)$ [(cf. equations (15) and (16)] are positive; consequently, $D(0\,, n-1)$ considered as a polynomial of n-th degree in s [cf. the denominators in equation (16)] has all its coefficients positive. Therefore, by Descartes' rule of signs, it has no positive or zero roots, and since all its roots are real, it must have all roots negative. It will appear from the following discussion that it is sufficient to consider three types of principal minors of $D_0(0\,, n-1)$:

(i). Consider first the minor consisting of the first r rows and columns, i.e.

$$D_0(0\,, r-1) = \begin{vmatrix} k_1\,, & g_0\,, & 0\,, & 0\,, & \cdot\ \cdot \\ k_1\,, & k_2 + g_0\,, & g_1\,, & 0\,, & \cdot\ \cdot \\ 0\,, & k_2\,, & k_3 + g_1\,, & g_2\,, & \cdot\ \cdot \\ \cdot\ \cdot & \cdot\ \cdot & \cdot\ \cdot & \cdot\ \cdot & \cdot\ \cdot \\ 0\,, & \cdot\ \cdot\ \cdot & k_{r-1}\,, & k_r + g_{r-2} & \end{vmatrix} , \tag{32}$$

and transform it by subtracting and by adding its rows in an alternating manner, i.e.: leave the first row as it is; subtract from the second row the first one; subtract from the third row the second row and add the first, etc. By known theorems we do not change the determinant by these transformations, but it is easy to see that the new determinant has all its elements below the principal diagonal equal to zero, and that the principal diagonal is $k_1\,, k_2\,, \cdots, k_r$. Consequently,

$$D_0(0, r-1) = k_1 k_2 \cdots k_r > 0 . \tag{33}$$

(ii). Consider now a principal minor obtained from $D_0(0, n-1)$ by omitting only a certain number of its first and of its last rows and columns. Such a principal minor is of the type [cf. equation (13)]

$$D_0(i, m) = \begin{vmatrix} k_{i+1} + g_{i-1}, & g_i, & 0, & 0, \ldots \\ k_{i+1}, & k_{i+2} + g_i, & g_{i+1}, & 0, \ldots \\ 0, & k_{i+2}, & k_{i+3} + g_{i+1}, & g_{i+2}, \ldots \\ \ldots & \ldots & \ldots & \ldots \\ 0, \ldots & \ldots & k_m, & k_{m+1} + g_{m-1} \end{vmatrix}, \tag{34}$$

where $i \geqq 1$, $m \leqq n-1$. This determinant may be represented as a sum of two determinants having their first rows $k_{i+1}, g_i, 0, 0, \cdots$ and $g_{i-1}, 0, 0, \cdots$ respectively, and all the remaining $m-i$ rows the same as in $D_0(i, m)$. The first of these determinants is of the type (32) and the second is easily seen to be $g_{i-1} D_0(i+1, m)$, so that by equation (33),

$$D_0(i, m) = k_{i+1} k_{i+2} \cdots k_{m+1} + g_{i-1} D_0(i+1, m). \tag{35}$$

We have directly from equation (34),

$$D_0(m, m) = k_{m+1} + g_{m-1} > 0 .$$

Consequently, the principle of mathematical induction applied to equation (35) shows that $D_0(i, m) > 0$.

(iii). The third type of principal minor which must be discussed is the one which is formed from $D_0(0, n-1)$ by omitting some of its intermediate rows and columns. Consider the case in which the omitted rows and columns are contiguous in the original determinant. Then it is easy to see that such a minor consists of four rectangular arrays, the elements of the left bottom array being all zero, and those of the left top and right bottom arrays forming each a determinant of the type (34) or (33). Therefore, the minor under consideration is a product of two determinants of the type (i) or (ii) and is consequently a positive quantity.

It is clear from the discussion of the last type of minor that any other principal minor of $D_0(0, n-1)$ is a product of some principal minors of the above three types and is consequently a positive number. In this way, the proof that the roots of equation (30), i.e. $-\bar{k}_1, -\bar{k}_2, \cdots, -\bar{k}_n$ are all real and negative is complete. But to obtain the equivalence theorem it is still necessary to show that between these roots and the original k_i's, the relation (28) holds. This is, however, an immediate consequence of the fact that

$$\bar{k}_1 \bar{k}_2 \cdots \bar{k}_n = [D(0, n-1)]_{s=0} = D_0(0, n-1),$$

which by equation (33) equals $k_1 k_2 \cdots k_n$.

The equivalence theorem which has just been proven shows that an analysis of experimental data on $Y_n(t)$ cannot give any direct information as to the recovery process if the intermediate states cannot be observed and no recovery occurs from the final state. Because of this latter condition the procedure of pure recovery consisting in obtaining experimental values of $Y_n(t)$ after the irradiation has been stopped (cf. Fano and Marinelli, 1943) cannot be applied here either, and the only method to separate the intensities of injury k_i from those of recovery g_i is to carry out experiments with various intensities of radiation J and to take into account the different dependence of the k_i's and g_i's on J (cf. equation (20) and the corresponding paragraph of Sec. 3).

As an example consider a process between three states 0, 1, 2, with 2 as the final state, from which no recovery occurs. By using the equivalence theorem, it is easy to see that such a process is equivalent, as far as the final state is concerned, to a process without recovery and with direct intensities:

$$\bar{k}_1 , \bar{k}_2 = K \pm (K^2 - k_1 k_2)^{1/2} , \qquad (36)$$

where $2K = k_1 + k_2 + g_0$. The case $k_1 = k_2$ is the one considered by W. Swann and C. Del Rosario (1931) and it may be easily checked that their formulae can be obtained by using the relations (36) and the general equations of processes without recovery (Opatowski, 1942). It may be seen from this example that the equivalence property as represented by relation (36) holds only for the resulting process between the initial and the final states but does not hold simultaneously between intermediate states. The property of *symmetry* of the final effect $Y_n(t)$ with respect to the direct intensities of the component processes is also clear from relation (36). In fact, this relation is symmetric in k_1 and k_2 as well as in $\bar{k}_1$ and $\bar{k}_2$.

We have considered up to now in this section a process (p) in which $k_{n+1} = g_{n-1} = 0$. If the n-*th state is final and recovery occurs from that state,* then $k_{n+1} = 0$ but $g_{n-1} \neq 0$. A theorem similar to the equivalence theorem may be formulated also in this case, although it expresses only a *proportionality* of the effect. The theorem may be stated as follows: A number N of microorganisms which are initially in a state 0 and are subject to a chain process (p) between the states $0, 1, \cdots, n$ involving direct and reverse transitions reaches the state n according to the same time relationship that an aggregate of a certain number $\bar{N}$ of the same microorganisms would pass from the state 0 to the state n if subject to a suitable chain process $(\bar{p})$ involving direct transitions only between the same number of states. The differ-

ences in reasoning which are necessary in the present case to prove the theorem in question are the following:

(a). Instead of $D(0, n; k_i, g_i)/s$, we consider now the determinant $D(0, n; k_i, g_i)$ with $2I_n = g_{n-1}$ [see equation (13)]. The expansion of this determinant as a polynomial of s has all its coefficients positive, except the term of degree 0 which equals $D_0(0,n)$ and consequently is zero by equation (33). Therefore, one of the roots of this polynomial is zero ($\bar{k}_{n+1} = 0$) and all the others $-\bar{k}_1, -\bar{k}_2, \cdots -\bar{k}_n$ are negative, as before. The n-th state is final in the $(\bar{p})$ process.

(b). The number of microorganisms which at $t = 0$ are in the state 0 of the process $(\bar{p})$ must be taken equal to

$$\bar{N} = (P_n/\bar{P}_n)N, \quad \text{where} \quad \bar{P}_n = \bar{k}_1 \bar{k}_2 \cdots \bar{k}_n,$$

and N is the initial number of microorganisms in the state 0 of the process (p). This change of the number of microorganisms is a consequence of the general expression of $y_n(s)$ [cf. equations (11), (12), and (28)]. To show that $\bar{N} \neq N$, and consequently that we have in the present case only a proportionality of the effects and not an equivalence of the processes (p) and $(\bar{p})$, we have still to prove that $\bar{P}_n \neq P_n$. This can be done in the following manner: since one of the roots of $D(0, n)$ is zero, $\bar{P}_n$, being the product of the non-zero roots of $D(0, n)$, is the coefficient of s in the polynomial expansion of $D(0, n)$, i.e., by equations (14) and (16),

$$\bar{P}_n = \sum_M M_n(0, n).$$

Now, all terms of this sum are non-negative. We show that one of them equals P_n, and at least one of the remaining is positive, consequently $\bar{P}_n > P_n$. In fact, the term which is obtained from $D_0(0, n)$ by omitting its last row and column is by equation (33)

$$D_0(0, n-1) = P_n.$$

The term which is obtained from $D_0(0, n)$ by omitting its n-th row and column is easily seen to be in the present case

$$(k_{n+1} + g_{n-1})\, D_0(0, n-2) = g_{n-1} k_1 k_2 \cdots k_{n-1} > 0.$$

In this way the relation $\bar{P}_n > P_n$, and consequently $\bar{N} < N$, is proved. Since the process $(\bar{p})$ occurs without recovery, it is intuitive that the initial number of its microorganisms in the state 0 must be smaller than in the process (p), which involves also recovery transitions.

If the n-*th state of the process* (p) *is not final and recovery occurs from that state,* then $k_{n+1} \neq 0$, $g_{n-1} \neq 0$. In this case all the $n+1$

roots $-\bar{k}_1$, $-\bar{k}_2$, $\cdots$ $-\bar{k}_{n+1}$ of $D(0,n)$ are negative. By equation (33) we have now

$$D_0(0\,,\,n) = \bar{k}_1\,\bar{k}_2 \cdots \bar{k}_{n+1} = k_1\,k_2 \cdots k_{n+1}\,,$$

so that the above relation of proportionality of the effects can now be written in the simple form

$$\bar{N} = (\bar{k}_{n+1}/k_{n+1})N\,.$$

In general, $\bar{k}_{n+1} \neq k_{n+1}$, but if $s = -k_{n+1}$ is a root of the polynomial $D(0\,,\,n;\,k_i\,,\,g_i)$, then taking this root as $-\bar{k}_{n+1}$ we have in the present case an actual equivalence theorem between the processes (p) and $(\bar{p})$. This requires, however, a particular relation between the intensities k_i and g_i of the original process (p), which may be obtained by putting $s = -k_{n+1}$ in the equation $D(0\,,\,n;\,k_i\,,\,g_i) = 0$.

We can now discuss the question in what cases a *complete transition of the whole aggregate of microorganisms* from the state 0 to the state n is possible. If the whole process occurs without recovery, i.e. if all g_i's are zero, and if the n-th state is final $(k_{n+1} = 0)$, we know that the transition tends to be complete as $t \to \infty$ because (cf. Opatowski, 1942, p. 87)

$$[Y_n(t;\,\bar{k}_i\,,\,0)]_{t\to\infty} = 1\,.$$

Therefore, a complete transition occurs also in the case in which recovery is possible between the intermediate states of the process (p) and $k_{n+1} = g_{n-1} = 0$. This is an immediate consequence of the equivalence theorem and of the equation (26).

In the case in which $k_{n+1} = 0$ but $g_{n-1} \neq 0$, a complete transition does not occur because we now have for the number of organisms in the state n

$$N[Y_n(t;\,k_i\,,\,g_i)]_{t\to\infty} = \bar{N}[Y_n(t;\,\bar{k}_i\,,\,0)]_{t\to\infty} = \bar{N} = (P_n/\bar{P}_n)N\,.$$

It has been shown that $P_n < \bar{P}_n$, therefore, not all microorganisms reach the state n even if $t \to \infty$. This is intuitive because recovery occurs here also from the final state.

If the complete process is without recovery and the n-th state is not final, the corresponding function $Y_n(t)$ tends to zero as t tends to infinity (cf. e.g. Lundberg, 1940, pp. 49-64). This is true also if there is recovery and $k_{n+1} \neq 0$, $g_{n-1} \neq 0$, because of the proportionality of the effects of processes (p) and $(\bar{p})$. Therefore, the microorganisms reach the state n up to a certain maximum number (which is necessarily smaller than N) and then decrease to zero as t increases indefinitely. There is one maximum only and its location in processes

of this type has been studied by O. Lundberg and W. Feller (see Lundberg, *loc. cit.*).

6. Processes with recovery barriers. If recovery is impossible between the states j and $j-1$, that is, if $g_{j-1}=0$ (cf. Sec. 2), then from equations (11) to (13)

$$y_n = P_n/[D(0,j-1)\,D(j,n)]\,, \tag{37}$$

because in the determinant $D(0,n)$ the elements of the first j rows and of the last $n-j+1$ columns are zero, so that $D(0,n)$ equals the denominator in equation (37). The recovery barrier between the states $j-1$ and j splits the given process into two component processes:

(1) the process which brings the organisms from the state 0 to the state $j-1$ with the direct and reverse intensities respectively equal to $k_1, k_2, \cdots k_j$; $g_0, g_1, \cdots g_{j-2}$ and

(2) the process which brings the organism from the state j to the state n with the intensities $k_{j+1}, \cdots k_n$; $g_j, \cdots g_{n-1}$.

Let $NY_{j,n}(t)$ be the number of organisms in the state n at the time t, under the assumption that at the time $t=0$, all the N organisms were in the state j. Let $NY_{0,j-1}(t)$ have a similar meaning for the first component process. We have then from equations (37), (11), and (12) and by a known theorem of the Laplace transformation (Doetsch, 1937, pp. 157, 163; Widder, 1941, pp. 91, 92; Churchill, 1944, p. 37),

$$Y_{0,n} = Y_{0,j-1} * Y_{j,n}\,, \tag{38}$$

where * is the known symbol of convolution defined by

$$\phi(t) * \psi(t) = \int_0^t \phi(\tau)\,\psi(t-\tau)\,d\tau\,. \tag{39}$$

In this section $Y_{0,i}$ is used for clarity instead of the previously used symbol Y_i.

All formulae of the previous sections are still valid in the present case, but if G means now the arithmetic average of those intensities of recovery which are presumed to be different from zero, then the term nG should be changed in equations (23) and (24) into $(n-1)G$.

The discussion of this section may be easily generalized to the case when recovery barriers exist between several states. One obtains instead of equation (38) the following formula:

$$Y_{0,n} = Y_{0,j-1} * Y_{j,m-1} * Y_{m,p-1} * \cdots * Y_{q,n}\,, \tag{40}$$

which appears as a generalization of a relation valid in the case in which the whole process goes on without recovery, that is, when recovery barriers exist between each two states (Opatowski, 1942, p. 85).

7. Organisms with more than one sensitive volume. To treat this case it is convenient to interpret the function $Y_i(t) \equiv Y_{0,i}(t)$ as a *probability* that a microorganism be at the time t in the state i if it is at the time $t = 0$ in the state 0 (cf. Opatowski, 1942, p. 84). Consider for simplicity the case of two sensitive volumes (v) and (w), and discuss first the case in which a certain effect (e) is reached in the organism when (v) is brought from a state 0 to a state p, and (w) from another state 0 to a state q. Assume that the changing of a state of either one of the two sensitive volumes is independent of the state of the other sensitive volume. Since a state i of the *microorganism* may be characterized as a simultaneous presence of (v) in a certain state p' and of (w) in a certain state q', it is clear that a microorganism may reach the effect (e) through different intermediate states (cf. Sec. 2), so that the theory developed in the previous sections cannot be applied without modification. This, however, can be easily obtained by probabilistic considerations. In fact, the probability $Y_{0;p,q}(t)$ that the microorganism shows at the time t the effect (e) if at the time $t = 0$ it was in the state 0: that is, if (v) and (w) were both in the state 0, is

$$Y_{0;p,q} = Y_{0,p}\, Y_{0,q} . \tag{41}$$

Equation (41) is substantially a formula of H. Bethe and W. Seyfarth (cf. Glocker, 1932). Instead of relation (25), we have in the present case

$$p + q = \lim_{t \to 0} [td \log_e Y_{0;p,q}(t) / dt] . \tag{42}$$

An application of the power series expansion (21) gives now

$$\begin{aligned} \log Y_{0;p,q} = \log P_{p+q} - \log (p!q!) + (p + q) \log t \\ + \log (1 + at + \cdots) , \end{aligned} \tag{43}$$

where $a = (p + 1)^{-1} a_{p,1} + (q + 1)^{-1} a_{q,1}$, and $a_{p,1}$, and $a_{q,1}$ have a similar meaning as $a_{n,1}$ defined by equation (22).

The case in which the effect (e) is reached when (v) reaches the state p or (w) reaches the state q may be treated in a similar manner on the basis of general theorems of probability.

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THE FLOW OF A VISCOUS FLUID IN AN ELASTIC TUBE: A MODEL OF THE FEMORAL ARTERY

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The solutions of the classical differential equations for flow of a viscous fluid in an elastic tube are shown to yield a description of some aspects of the flow of blood in the femoral artery. The parameters influencing the speed of the pulse wave, the pressure, and the velocity for non-pulsating and pulsating flow are exhibited. The relation between pressure and velocity are considered in some detail. It is shown that for pulsating flow the slope of the pressure versus fluid velocity curve is equal to the pulse wave speed multiplied by the density of the blood.

The mathematical treatment of blood circulation has the usual intractable features of general hydrodynamics as mentioned by N. Rashevsky (1945a, b) further complicated by such factors as the variation of the viscosity and of the compressibility of the blood mainly due to the corpuscular structure, as well as by the nervous and the chemical control of the size of the blood vessels. In spite of the present impossibility of even a good approximate general treatment, the classical equations do yield results which have significance for the physiologist and biophysicist.

This paper discusses the equation of flow of a viscous fluid in an elastic tube and uses data on flow in the femoral artery to test the solutions.

The Differential Equations of Flow:

The equations for this problem may be derived by the usual methods as exemplified by O. Frank (1926) or A. Foch (1932). The equations are

$$\rho \frac{\partial u}{\partial t} + \frac{\partial p}{\partial x} = \mu \nabla^2 u, \tag{1}$$

$$\rho \frac{\partial u}{\partial x} + \frac{1}{v^2} \frac{\partial p}{\partial t} = 0, \tag{2}$$

where

$u =$ velocity along the axis of the tube (In x-direction)

$p =$ pressure
$\rho =$ density of fluid
$\mu =$ viscosity of fluid
$E =$ the modulus of elasticity of the tube wall
$\nabla^2 u =$ the Laplacian of u
$K =$ the compressibility of the blood
$e =$ thickness of the tube wall
$r_0 =$ radius of the unstretched tube.

In our treatment, ρ is constant and, therefore, $K = 0$.
Differentiating equation (1) with respect to t and equation (2) with respect to x, and eliminating the p-term, we find

$$\rho \frac{\partial^2 u}{\partial t^2} = \rho v^2 \frac{\partial^2 u}{\partial x^2} + \mu \frac{\partial}{\partial t} (\nabla^2 u).$$

On expressing the Laplacian in cylindrical coordinates and substituting $u = C \exp(-\alpha t - \beta x) R(r)$, we are led to Bessel's equation for $R(r)$ (Von Kárman and Biot, 1940),

$$\frac{d^2 R}{d r^2} + \frac{1}{r} \frac{d R}{d r} + \lambda^2 R = 0 ,$$

where

$$\mu \alpha \lambda^2 = \rho \alpha^2 + (\mu \alpha - \rho v^2) \beta^2. \tag{3}$$

The final solution is then

$$u = \exp(-\alpha t - \beta x) [C_1 J_0(\lambda r) + C_2 Y_0(\lambda r)] . \tag{4}$$

Inasmuch as u must be finite at the axis and since

$$Y_0(\lambda r) \to -\infty \quad \text{as} \quad r \to 0 , \quad C_2 = 0 .$$

the complete solution is therefore

$$u = \sum_{n=1}^{\infty} C_n J_0(\lambda_n r) \exp(-\alpha_n t - \beta_n x) . \tag{5}$$

In our flow problem, we are primarily interested in the pulse wave speed, the pressure, and the fluid velocity.

The speed of the pulse wave:

If we are treating flow of a non-viscous fluid, the μ-term on the right of equation (1) would be absent. Elimination of the u-term between equations (1) and (2) would lead to the wave equation for p where the speed of propagation of the pressure wave, v, would be given by

$$v = \sqrt{\frac{e E}{2 \rho r_0}} . \tag{6}$$

This is the well-known Moens' equation (Moens, 1878). Although derived for a non-viscous liquid, it has been found to apply quite satisfactorily to viscous flow.

In the v-equation we seem to have a valuable equation for finding a relation among some physically significant parameters (e, E, ρ, r_0). These parameters are, however, most difficult to measure and even to define satisfactorily. J. C. Bramwell and A. V. Hill (1922) found that Moen's equation held for flow in an artery but they transformed it by replacing the original parameters by the compressibility of the artery which is more easily measured:

$$v = 0.357 \sqrt{V \frac{dp}{dV}},$$

where p is measured in mm of mercury (Hg), V is the volume per unit length of the artery, and v is in meters/sec.

Non-pulsating flow:

The elastic tube is connected to a reservoir where the pressure may be maintained constant for any desired length of time (i.e., at $x = 0$, $p = p_1$, for all t's). The tube will stretch to some maximum radius, b. At the tube wall ($r = b$) we assume the usual Poiseuille condition, $u = 0$, hence

$$J_0(\lambda b) = 0. \tag{7}$$

Using equation (3) and equations (2), we get for the pressure

$$p = f(x) - \frac{v^2 \rho \beta}{\alpha} u. \tag{8}$$

At the wall $r = b$, $u = 0$ and

$$f(x) = p_b.$$

But also at wall, the pressure is distributed in overcoming the tension of the walls and the outside pressure, so

$$p_b = p_0 + e E \left(\frac{1}{r_0} - \frac{1}{b} \right), \tag{9}$$

where p_0 is the pressure in the medium surrounding the tube. If b varies along the tube, as it probably will, p_b is not constant. For variable b there would have to be a different value of λ for each point. A more tractable procedure would be to treat the tube as composed of sections of constant radii, but the radii decreasing as we go from section to section. For each section then there would be a series of solutions corresponding to equation (7) for the radius of that sec-

tion. There is, however, no need for our doing that for this discussion.

The data of S. R. F. Whittaker and F. R. Winton (1933) may be used to test equations (3) and (8). Whittaker and Winton (1933) perfused the hind leg of a dog with whole blood through the femoral artery and recorded the relation between pressure and velocity of flow. The flow took place through the entire complex of artery, connecting arterioles, capillaries, and finally into the veins which were cut to allow the liquid to run into a collector. The equations used in our derivation are for a single vessel; hence, in all correctness, we may consider our theory as yielding the *single vessel equivalent* of their complex system.

Their data may be expressed approximately as

$$\bar{p} = 20 + \tfrac{1}{2}\bar{u}\,, \tag{10}$$

where $\bar{p}$, the average pressure in the cross-section of the artery, is in mm of H_g and $\bar{u}$ is in cc/sec while our p is in dynes/cm^2 and u is in cm/sec. Using equation (4), we have for the flow in cc/sec,

$$u = 2\pi \int_0^b rudr = \sum_{n=1}^{\infty} 2\pi C_n \exp(-\alpha_n t - \beta_n x) \int_0^b r J_0(\lambda_n r)\, dr\,,$$

since

$$\frac{d}{dx}[x^m J_m(x)] = x^m J_{m-1}(x)\,.$$

We have corresponding to equation (5)

$$\bar{u} = 2\pi b \sum_{n=1}^{\infty} C_n \lambda_n^{-1} J_1(\lambda_n b) \exp(-\alpha_n t - \beta_n x)\,, \tag{11}$$

where the $J_m(x)$ is the Bessel function of the first kind of order m (Von Kárman and Biot, 1940).

Equation (11) should be able to satisfy the conditions here imposed and the pressure equation derived from it should satisfy at least approximately the condition $\bar{p} = p_1$ at $x = 0$ for all t.

The relation between $\bar{p}$ and $\bar{u}$ is of the same type as that between p and u, that is, equation (8). We see then that α and β may both be real, that β is negative and that

$$-\frac{v^2 \rho \beta}{\alpha} = \frac{1}{2}\left(\frac{1333}{\pi b^2}\right).$$

The preceding equation relates α and β. From the roots of equation (7): $\lambda_1 = 2.40/b$; $\lambda_2 = 5.52/b$, $\cdots$, $\cdots$ we have the various λ's to be substituted into equation (3) so that we may determine both α and

β in terms of ρ, v, μ, and b. The algebraic expressions are easily obtained and show that there is a choice of sign so that $\alpha > 0$ and that α varies inversely as μ.

Although the preceding analysis seems quite adequate for a description of the flow in the hind leg of a dog, so far as the relation between pressure and velocity for non-pulsating flow, the data of T. E. Machella (1933) reveal that p and u are also *linearly* related for the femoral artery proper. His data were for pulsating flow, which we shall consider in the next section.

Pulsating Flow:

In pulsating flow, the pressure and velocity are some periodic functions of time and possibly also of position. We assume that velocity, u, and pressure, p, may be represented as a Fourier series of time. In order that our solution may be amenable to such expression, we may take

$$\alpha = a + i\,\omega \quad \text{and} \quad \beta = l + i\,m\,.$$

Equation (3) becomes on equating real and imaginary parts

$$\begin{aligned} \mu\,\lambda^2\,a &= \rho(a^2 - \omega^2) + (\mu\,a - \rho\,v^2)(l^2 - m^2) - 2\,\mu\,l\,m\,k\,, \\ \mu\,\lambda^2\,\omega &= 2\,\rho\,a\,\omega + 2\,l\,m(\mu\,a - \rho\,v^2) + \mu\,\omega(l^2 - m^2)\,. \end{aligned} \tag{12}$$

The velocity must be zero at the wall as before; thus λ will again satisfy equation (7). We still have four parameters (a, ω, l, m) and two equations (12) besides the boundary conditions.

T. E. Machella (1936) gave curves showing the relation between the velocity and pressure curves at the same point in the femoral artery (see his Figure 7). The curves have the same shape, but the numerical values of maxima and minima differ. We shall show that solution for u fits his data. We may write

$$u = \sum_{n=1}^{\infty} F(x_1\, r)\, \exp(-a_n\, t)\, [C_n \cos \omega_n\, t + C_n' \sin \omega_n\, t]\,.$$

Since x is fixed and r may be considered as constant, we must ascertain whether a u of the form

$$u = \sum_{n=1}^{\infty} \exp(-a_n\, t)\, [C_n \cos \omega_n\, t + C_n' \sin \omega_n\, t]$$

can fit Machella's results for both u and p. We have a choice. Either we may fit our u for a single cycle of systole and diastole or fit a complete curve of many similar cycles. If we choose to find u for the general curve with many cycles, $a_n = 0$, and our problem becomes one

of finding the C_n and C_n' to fit the experimental data by harmonic analysis. The author reproduced Machella's curve for u and p found the coefficients by a numerical method (Von Kárman and Biot, 1940). By taking a sufficiently large number of terms the series may be made to fit as closely as desired.

The expression for p is from equation (8)

$$p = \frac{v^2 m \rho}{\omega} u + p_b. \tag{13}$$

Thus if the velocity, u, can be expressed as a Fourier series with real coefficients, the pressure, p, must be expressed by the same series with each coefficient multiplied by a constant factor. Machella's p ranges from 88 to 156 mm of Hg and his u from 5 to 93 cm/sec. These two points are sufficient, of course, to determine the slope and intercept in equation (13). However, equations (1) and (2) are not applicable for the assumption that $a_n = 0$ involves a non-viscous fluid, for in order to satisfy equation (3) and the experimental conditions, it is necessary that $\mu = l = 0$ which is the non-viscous flow problem. The relation between p and u is still given by equation (13). But the differential equation now requires that

$$\omega = v m,$$

so that equation (10) becomes

$$p = (v \rho) u + p_b. \tag{14}$$

Machella's (1936) curve 7 gives

$$\bar{p} = 0.773 u + 84.13,$$

where $\bar{p}$ is in mm of Hg. In order to compare with equation (14) we must multiply by (1,013,000/760) to convert p to dynes/cm^2. We have then

$$p = 1020u + 110{,}000.$$

Therefore, the Fourier Series calculated for u gives p through this linear equation. Probably the most interesting aspect is that the *slope of the* p—u *curve gives the speed of the pulse wave*, for since $\rho \approx 1$, the slope is very nearly v. In Machella's (1936) experiment we have that $v = 10$ meters/sec which is a reasonable value. Alternately knowing v, we can calculate the compressibility or the other parameters from Moens' equation.

The preceding analysis is not quite as attractive as it seems, for the pulse velocity has been found to vary with the pressure. J. C. Bramwell and A. V. Hill's (1922) values for pulse velocity as a func-

tion of effective pressure, $(p - p_0)$, of an excised section of artery reveals that as $(p - p_0)$ varies from 0 to 70 mm of Hg, the pulse velocity goes from 1.5 to 4.9 meters/sec. This experiment was for non-pulsating flow and is relevant to our equation (9). We cannot explain the variation, however, by a mere increase in radius, since the velocity for the unstretched tube, is too small ($v_0 = 1.5$ meters/sec). The logical explanation is that the elasticity, E, varies with pressure. Equation (9) is still valid physically; and it can be used to determine the variation of E with effective pressure by measuring the radius. Equation (14) is still valuable in that it yields an approximate value of the pulse velocity.

If we are interested in finding u for one cycle only, we may take $a_n \neq 0$, and we have a slightly more difficult problem in harmonic analysis. From Machella's (1936) data, we may determine the coefficients of u. In place of equation (13) we have

$$p = \frac{v^2 \rho (a l + m \omega)}{a^2 + \omega^2} u + p_b.$$

In order that p may be real the imaginary part of p must vanish:

$$l \omega = a m. \tag{15}$$

The coefficient of u here must equal 1020 gm/sec cm^2 as before. The equation resulting from equating the coefficient to 1020 gm/sec cm^2 with the equations (5), (7) and (15) determine the relations among the parameters, a, l, m, λ (since ω is determined by the period of the cycle), and ρ, v, and μ.

Although the solution for a single cycle may initially seem rather artificial, the fact that it involves the complete equation recommends it to the author. We look upon the flow as being initiated at each systole, continuing the diastole and the values of u and p being altered by the characteristics of the elastic tube (the femoral artery).

It is interesting to note that Machella's pressure—velocity curves for the carotid artery do not show similarity of shape. This lack of similarity may be explained by the nearness of the carotid to the heart, thus the surge is so great that the approximations inherent in our differential equations are much too crude.

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BULLETIN OF
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A CONTRIBUTION TO THE MATHEMATICAL BIOPHYSICS OF CELL GROWTH AND SHAPES: I

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Under the assumption that the elongated shape assumed by a growing nerve cell is caused by surface tension forces between the cell, its fluid medium, and a fibrous substrate track along which the cell grows, equations of elongation and conditions insuring elongation are derived. One specific type of cell-substrate contact is considered. Equations of elongation and conditions for elongation are treated in both the non-frictional and frictional types of motion of the cell-process.

In this paper we propose to develop a theory of the growth of nerve fibers. We shall explore the consequences of various assumed relations between the physical factors such as interfacial tensions, cell volumes and shapes, etc., which might plausibly enter as determining this growth.

At this point of theoretical investigation, we are chiefly interested in the role played by these physical factors when related in certain ways. In order to discover the influence any one of these factors may exert, a thorough study of many cases must be attempted.

Certain conclusions will be forthcoming which may aid in enabling us to decide the basic question of the mechanism of the growth of nerve cells, both in the living organism and in the tissue culture.

The growth of nerve fibers in tissue cultures has been described by P. Weiss (1934, 1941) as a drawing out of elongated threads, called filopods, from the central body of the cell.

These elongated threads grow out along fiber tracks which are produced from an exudate originating from the cells in the culture.

We shall discuss the process of growth of a filopod under the following conditions: (1) the growing cell-process may be considered as a viscous thread approximately cylindrical in shape in contact with the substrate fiber; (2) interfacial tension forces at the interfaces of cell-process, culture medium, and substrate fiber are predominant in causing elongation of the cell-process; (3) the volume of the cell-process remains constant during elongation.

I

We shall first suppose that the cell-process makes contact with the substrate fiber along a thin strip. Figure 1 shows both a longi-

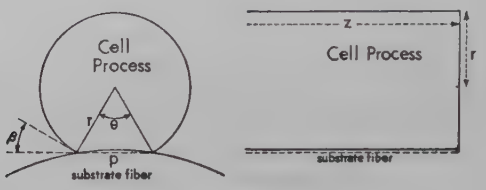

FIGURE 1

tudinal and cross-section of the cell-process and substrate in this case. We assume that the radius of the substrate fiber is much greater than the radius of the cell-process. Hence we may consider the surface of contact between cell-process and substrate approximately as a flat rectangle.

We denote by

p = width of the cell-substrate interface
r = radius of cell-process
z = length of cell-process
θ = angle subtended by p
β = angle of contact of cell-process with substrate.

It has been suggested that the filopod grows because it is "pulled in" between the substrate and the medium, in a process similar to wettening. But in such a case an isotropic interfacial tension would result in the spreading of the cell material in a thin layer all over the interface between medium and substrate. A growth in *one* direction is possible only if the interfacial tension at least between two of the three component materials is anisotropic. Inasmuch as the substrate is supposed to consist of oriented long-chain molecules, this unavoidable anistropy is made physically plausible. In this case, the interfacial tension becomes a two-dimensional tensor. Approximately we shall treat the problem as if we had simply two distinct interfacial tensions in two perpendicular directions.

Let us denote by Γ_{cs} the interfacial tension of the cell-substrate (cs) interface parallel to the z-direction and by γ_{cs} the interfacial tension of the cs interface normal to the z-direction.

We also denote by Γ_{ms} the interfacial tension of the medium-substrate (ms) interface parallel to the z-direction and by γ_{cm} the interfacial tension of the cell medium (cm) interface in any direction.

Let us denote by

$$\left.\begin{aligned} S_{cs} &= \text{area of } cs \text{ interface} = zp \\ S_{ms} &= \text{area of } ms \text{ interface} \\ S_{cm} &= \text{area of } cm \text{ interface} = \tfrac{1}{2}r^2(2\pi - \theta) + r(2\pi - \theta)z \end{aligned}\right\}. \quad (1)$$

From elementary geometry we have $\theta = 2\beta$, and since β is an angle of contact, we may assume that it, and hence θ, are constant. Thus from expression (1) we have

$$dS_{cs} = zdp + pdz, \quad (2)$$

and

$$dS_{cm} = 2(\pi - \beta)[rdz + (z + r)dr]. \quad (3)$$

In equation (3), $z >> r$ and $dz >> dr$, hence we may ignore the term rdr and obtain

$$dS_{cm} = 2(\pi - \beta)(rdz + zdr). \quad (4)$$

We also have

$$dS_{ms} = -dS_{cs} = -zdp - pdz. \quad (5)$$

From Figure 1 we see that

$$p = 2r \sin \beta, \quad (6)$$

thus equation (2) becomes

$$dS_{cs} = 2r \sin \beta\, dz + 2z \sin \beta\, dr. \quad (7)$$

In equation (7) the part $2r \sin \beta\, dz$ represents an increment of S_{cs} in the z-direction while $2z \sin \beta\, dr$ represents an increment of S_{cs} normal to z.

If we denote by dE the change in energy resulting from a change in length dz, we have from equations (4), (5), (6) and (7):

$$\begin{aligned} dE = {} & 2r[\sin \beta(\Gamma_{cs} - \Gamma_{ms}) + \gamma_{cm}(\pi - \beta)]\, dz + \\ & 2z[\sin \beta(\gamma_{cs} - \Gamma_{ms}) + \gamma_{cm}(\pi - \beta)]\, dr. \end{aligned} \quad (8)$$

The relation between z and r is given by

$$r^2(\pi - \beta)z = V = \text{volume of cell process}, \quad (9)$$

and since V is assumed constant, we have

$$dz = -\frac{2Vdr}{(\pi - \beta)r^3}. \quad (10)$$

Combining equations (8), (9), and (10) gives

$$dE = -4[\sin\beta(\Gamma_{cs} - \Gamma_{ms}) + \gamma_{cm}(\pi - \beta)]\frac{Vdr}{r^2(\pi - \beta)} + \frac{2V}{r^2(\pi - \beta)}[\sin\beta(\gamma_{cs} - \Gamma_{ms}) + \gamma_{cm}(\pi - \beta)]\,dr. \tag{11}$$

If the process is to elongate spontaneously, its elongation must be accompanied by a decrease in energy. Hence

$$dE < 0\,. \tag{12}$$

Since $V > 0$, $r^2 > 0$, and $\beta < \pi$, equation (11) implies that inequality (12) is equivalent to

$$\{-2[\sin\beta(\Gamma_{cs} - \Gamma_{ms}) + (\pi - \beta)\gamma_{cm}] + [\sin\beta(\gamma_{cs} - \Gamma_{ms}) + (\pi - \beta)\gamma_{cm}]\}\,dr < 0\,. \tag{13}$$

In order to have elongation, we must have $dz > 0$, or, because of equation (10), $dr < 0$. Thus in order that inequality (12) holds, we must have:

$$\sin\beta(\gamma_{cs} + \Gamma_{ms} - 2\Gamma_{cs}) - (\pi - \beta)\gamma_{cm} > 0\,. \tag{14}$$

Since inequality (14) is independent of r and z, we may conclude that *once elongation begins it will continue until the end of the substrate is reached.*

This conclusion is limited by the fact that as r approaches a magnitude comparable to molecular dimensions the preceding analysis of surface tensions is inadequate and equation (8) does not hold.

We shall now derive an equation giving z as a function of the time t. We must at first content ourselves with such an equation of elongation as can be derived assuming that $z = z_0$ when $t = 0$, where z_0 itself represents an elongation sufficient to make the cell-process cylindrical.

As a first approximation, we may consider the filopod as a viscous thread, pulled by a force concentrated at its end and equal to $-dE/dz$, choosing the direction of elongation as positive. Denoting by η the viscosity of the thread and by A_0 and z its cross-sectional area and length respectively, we have (Nadai, 1928)

$$\frac{1}{z}\frac{dz}{dt} = \frac{1}{3\eta}\frac{-dE/dz}{A_0}. \tag{15}$$

In our case, A_0 is given by

$$A_0 = r^2(\pi - \beta), \tag{16}$$

while $-dE/dz$ is given by equation (8) as

$$\frac{-dE}{dz} = -2r[\sin\beta(\Gamma_{cs} - \Gamma_{ms}) + \gamma_{cm}(\pi - \beta)] - 2z[\sin\beta(\gamma_{cs} - \Gamma_{ms}) + \gamma_{cm}(\pi - \beta)]\frac{dr}{dz}. \tag{17}$$

Combining equations (17), (10), and (9), we obtain

$$-\frac{dE}{dz} = r[(\gamma_{cs} + \Gamma_{ms} - 2\Gamma_{cs})\sin\beta - (\pi - \beta)\gamma_{cm}]. \tag{18}$$

Combining equations (18), (16), (15), (10), and (9), we have

$$-6\eta(\pi - \beta)\frac{dr}{dt} = \sin\beta(\gamma_{cs} + \Gamma_{ms} - 2\Gamma_{cs}) - (\pi - \beta)\gamma_{cm}. \tag{19}$$

Putting

$$\frac{\sin\beta(\gamma_{cs} + \Gamma_{ms} - 2\Gamma_{cs}) - (\pi - \beta)\gamma_{cm}}{-6\eta(\pi - \beta)} = Q_0, \tag{20}$$

we have

$$\frac{dr}{dt} = Q_0. \tag{21}$$

Integrating equation (21) gives

$$r = Q_0 t + r_0. \tag{22}$$

From inequality (14) and equation (20), we see that $Q_0 < 0$. From equation (22) it follows that after $t = -r_0/Q_0$ seconds $r = 0$ (and hence, $z = \infty$). Actually, however, as r approaches molecular dimensions, equation (22) does not hold.

From equations (9) and (22) we obtain

$$z = \frac{V}{(\pi - \beta)(r_0 + Q_0 t)^2}. \tag{23}$$

In Figure 2 a graph of z is drawn according to equation (23). The

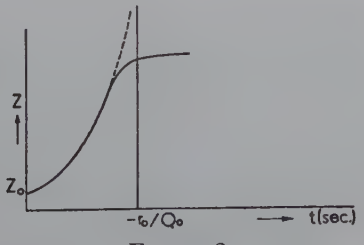

FIGURE 2

dotted line represents equation (23), whereas the solid line takes into account the fact that elongation ceases as r approaches molecular dimensions.

In the preceding discussion, the possible effect of all frictional forces was not considered. The internal friction present in an elongating viscous body is taken into account by equation (15).

The coefficients Γ_{cs} and γ_{cs} measure the net amount of attractive force between the molecules of substrate and cell. As the cell-process elongates, the number of molecules within the cell which are brought sufficiently near the substrate for molecular attractive forces to affect them increases. Thus the total net attractive force between cell-process and substrate increases proportionally to S_{cs}.

We may take into account this change by considering the net attractive force between substrate and cell as a normal force acting to produce a frictional drag force upon the cell-process. Since the coefficient of static friction μ_{cs} is given by (Foley, 1941)

$$\mu_{cs} = f/F_n , \tag{24}$$

where F_n is the net attractive force between cell and substrate, and where f is the frictional force, we may write

$$f = \mu_{cs} k_{cs} S_{cs} . \tag{25}$$

In equation (25) k_{cs} is a constant of proportionality. Assuming that the coefficient of static friction is constant and putting

$$f_0 = \mu_{cs} k_{cs} , \tag{26}$$

then from equations (25), (1), and (6), we have

$$f = 2 f_0 z r \sin \beta . \tag{27}$$

The force F' stretching the thread is then given by equations (27) and (18) as

$$F' = r[(\gamma_{cs} + \Gamma_{ms} - 2\Gamma_{cs}) \sin \beta - (\pi - \beta)\gamma_{cm} - 2 f_0 z \sin \beta]. \tag{28}$$

The expression (28) now takes the place of $-dE/dz$ in equation (15). Combining equations (15), (16), and (28) and putting

$$\frac{(\gamma_{cs} + \Gamma_{ms} - 2\Gamma_{cs}) \sin \beta - (\pi - \beta)\gamma_{cm}}{3\eta\sqrt{(\pi - \beta)V}} = R_0 , \tag{29}$$

and

$$\frac{-2 f_0 \sin \beta}{3\eta\sqrt{(\pi - \beta)V}} = S_0 , \tag{30}$$

we obtain

$$\frac{dz}{dt} = z^{3/2}(R_0 + S_0 z). \tag{31}$$

Equation (31) is in a convenient form for purposes of comparing theory with experiment. Setting $dz/dt = 0$ in equation (31), we find as a final value for z

$$z_f = -\frac{R_0}{S_0} = \frac{(\gamma_{cs} + \Gamma_{ms} - 2\Gamma_{cs}) \sin\beta - (\pi - \beta)\gamma_{cm}}{2f_0 \sin\beta}. \tag{32}$$

Since elongation, even when frictional drag is not considered, is possible only if equation (14) holds, we may state that equation (14) must hold also in the present case for elongation to occur, and therefore, $-R_0/S_0 > 0$. Hence if

$$-\frac{R_0}{S_0} > z_0 > 0, \tag{33}$$

then $dz/dt > 0$ by equation (31) and z will increase until $z = -R_0/S_0$. The same result for a final value of z is obtained by making use of equation (28) and

$$F' = -\frac{dE}{dt}, \tag{34}$$

as well as the conditions $dE < 0$, $dz > 0$.

Integration of equation (31) gives

$$\frac{2}{R_0\sqrt{z}} - \frac{\sqrt{-S_0}}{R_0\sqrt{R_0}} \log \frac{R_0 + \sqrt{z}\ \sqrt{-R_0S_0}}{R_0 - \sqrt{z}\ \sqrt{-R_0S_0}} = -t + h_0, \tag{35}$$

where

$$h_0 = -\frac{2}{R_0\sqrt{z_0}} - \frac{\sqrt{-S_0}}{R_0\sqrt{R_0}} \log \frac{R_0 + \sqrt{-z_0R_0S_0}}{R_0 - \sqrt{-z_0R_0S_0}}. \tag{36}$$

II

A different type of cell-substrate interface arises when the cell-process, acted upon by *isotropic* interfacial tensions, surrounds the substrate fiber completely. Denoting by a the radius of the substrate fiber and by r the radius, measured from the center of the substrate fiber, of the cell-process which may be approximated by a cylindrical sheath covering the substrate, we have

$$S_{cm} = 2\pi rz + \pi(r^2 - a^2), \tag{37}$$

and

$$S_{cs} = 2\pi az \,. \tag{38}$$

Hence

$$dS_{cm} = 2\pi r dz + 2\pi z dr + 2\pi r dr \,, \tag{39}$$

and

$$dS_{cs} = -\, dS_{ms} = 2\pi a dz \,. \tag{40}$$

In equation (39) we may drop the insignificant term $2\pi r dr$ since $z >> r$, obtaining

$$dS_{cm} = 2\pi r dz + 2\pi z dr \,. \tag{41}$$

Because of equations (40) and (41) the change in energy dE due to a change in length dz is given by

$$dE = 2\pi a (\gamma_{cs} - \gamma_{ms}) dz + 2\pi \gamma_{cm} (r dz + z dr) \,. \tag{42}$$

The volume of the cell-process is equal to

$$V = \pi (r^2 - a^2) z \,, \tag{43}$$

hence, since $V = \text{const.}$,

$$dr = -\frac{V}{2\pi r z^2} dz. \tag{44}$$

In view of equation (44), equation (42) becomes

$$dE = 2\pi a (\gamma_{cs} - \gamma_{ms}) dz + 2\pi \gamma_{cm} (r - \frac{V}{2\pi r z}) dz. \tag{45}$$

As before, $dE < 0$, consequently since $dz > 0$ for elongation, we must have as an inequality equivalent to $dE < 0$

$$2\pi a (\gamma_{cs} - \gamma_{ms}) + 2\pi \gamma_{cm} (r - \frac{V}{2\pi r z}) < 0. \tag{46}$$

In view of equation (43), inequality (46) is equivalent to

$$r + \frac{a^2}{r} < \frac{2a}{\gamma_{cm}} (\gamma_{ms} - \gamma_{cs}) \,. \tag{47}$$

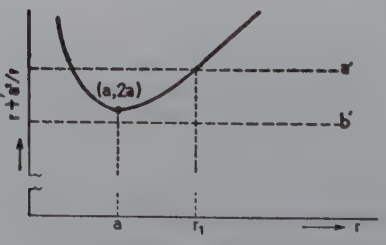

FIGURE 3

In Figure 3 the expression $r + a^2/r$ (the heavy line) is plotted against r. Since

$$\frac{d}{dr}\left(r + \frac{a^2}{r}\right) = 1 - \frac{a^2}{r^2}, \tag{48}$$

we have a minimum value of $r + a^2/r$ at $r = a$. At $r = a$ we have an ordinate of $2a$. The dotted line a' represents the value of $2a(\gamma_{ms} - \gamma_{cs})/\gamma_{cm}$ for $(\gamma_{ms} - \gamma_{cs})/\gamma_{cm} > 1$. The dotted line b' represents the value of $2a(\gamma_{ms} - \gamma_{cs})/\gamma_{cm}$ for $(\gamma_{ms} - \gamma_{cs})/\gamma_{cm} < 1$. For $(\gamma_{ms} - \gamma_{cs})/\gamma_{cm} < 1$, inequality (47) cannot hold and thus elongation cannot occur.

However, if $(\gamma_{ms} - \gamma_{cs})/\gamma_{cm} > 1$, elongation can occur provided $a < r < r_1$. If r—a is of molecular dimensions, the basic assumptions are invalid. If $r > r_1$, contraction ($dz < 0$) will result rather than elongation. Once elongation begins, it continues until either the end of the substrate fiber is reached, or until r—a approaches molecular dimensions.

From equation (45) and (43), we obtain

$$-\frac{dE}{dz} = -2\pi a(\gamma_{cs} - \gamma_{ms}) - \pi\gamma_{cm}\left(\frac{r^2 + a^2}{r}\right). \tag{49}$$

Combining equations (49), (43), and (44) with equation (15) and the equation for the cross-sectional area in the present case,

$$A_0 = \pi(r^2 - a^2), \tag{50}$$

gives

$$r\frac{dr}{dt} = -\frac{a}{3\eta}(\gamma_{ms} - \gamma_{cs}) + \frac{\gamma_{cm}}{6\eta}\left(\frac{r^2 + a^2}{r}\right). \tag{51}$$

Putting

$$A = -\frac{a}{3\eta}(\gamma_{ms} - \gamma_{cs}), \quad B = \frac{\gamma_{cm}}{6\eta}, \tag{52}$$

equation (51) becomes

$$\frac{r^2 dr}{r^2 + \frac{A}{B}r + a^2} = B dt. \tag{53}$$

Integrated, equation (53) gives

$$r - \frac{A}{2B}\log\left(r^2 + \frac{A}{B}r + a^2\right) + \frac{\frac{A^2}{B^2} - 2a^2}{\sqrt{4a^2 - \frac{A^2}{B^2}}}\tan^{-1}\frac{2r + \frac{A}{B}}{\sqrt{4a^2 - \frac{A^2}{B^2}}} = Bt + k_0, \tag{54}$$

where

$$k_0 = r_0 - \frac{A}{2B}\log\left(r_0^2 + \frac{A}{B}r_0 + a^2\right) + \frac{\frac{A^2}{B^2} - 2a^2}{\sqrt{4a^2 - \frac{A^2}{B^2}}}\tan^{-1}\frac{2r_0 + \frac{A}{B}}{\sqrt{4a^2 - \frac{A^2}{B^2}}}. \tag{55}$$

Equation (54) is inconvenient for purposes of testing the theory. In theory we may obtain t as a function of z by introducing equation (43) into equation (54). Inspection of equation (51) shows that dr/dt is not equal to zero for $r = a$ unless $\gamma_{ms} - \gamma_{cs} = \frac{1}{2}\gamma_{cm}$. Therefore, we cannot expect the theory to have any physical significance over the entire range $r \geqq a$. Another consideration limiting the theory is the fact that as r—a approaches molecular dimensions, the basic assumptions are no longer valid.

An equation giving dz/dt as a function of z may be obtained in the same way as was equation (51) except that r is eliminated instead of z. We have

$$\frac{dz}{dt} = \frac{2\pi a}{3\eta V}(\gamma_{ms} - \gamma_{cs})z^2 - \frac{\pi\gamma_{cm}}{3\eta V}z^2\left(\sqrt{a^2 + \frac{V}{\pi z}} + \frac{a^2\sqrt{\pi z}}{\sqrt{a^2\pi z + V}}\right). \tag{56}$$

Equation (56) might prove to be more convenient than an equation $t = t(z)$ for purposes of testing.

III

Considering a frictional drag force of f_0 dynes per sq cm of S_{cs} acting on the cell-process, the total force T pulling on the process is given by

$$T = -\frac{dE}{dz} - 2\pi a f_0 z. \tag{57}$$

In order that elongation occur, this force must be positive, in other words, that

$$-\frac{dE}{dz}-2\pi a f_0 z>0. \tag{58}$$

Hence, for $dz>0$

$$-\frac{dE}{dz}>2\pi a f_0 z. \tag{59}$$

Combining equations (45) and (43) with inequality (59), we have

$$\frac{a(\gamma_{ms}-\gamma_{cs})}{\gamma_{cm}}>\left(r+\frac{a^2}{r}\right)+\frac{2af_0}{\pi V(r^2-a^2)\gamma_{cm}}, \tag{60}$$

as an inequality equivalent to inequality (59).

Denoting

$$\psi(r)=r+\frac{a^2}{r}+\frac{2af_0}{\pi V\gamma_{cm}(r^2-a^2)}. \tag{61}$$

The general shape of the function $\psi(r)$ is represented graphically in Figure 4.

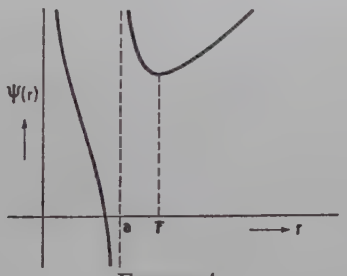

FIGURE 4

From equation (61) we obtain

$$\frac{d\psi(r)}{dr}=1-\frac{a^2}{r^2}-\frac{4af_0 r}{\pi V\gamma_{cm}(r^2-a^2)^2}. \tag{62}$$

Setting $d\psi(r)/dr=0$, we have

$$\frac{r^2-a^2}{r^2}=\frac{4af_0 r}{\pi V\gamma_{cm}(r^2-a^2)^2}. \tag{63}$$

Equation (63) becomes

$$(r^2-a^2)^3=r^3\frac{4af_0}{\pi V\gamma_{cm}}. \tag{64}$$

Denoting

$$s_0 = + \sqrt[3]{\frac{4af_0}{\pi V \gamma_{cm}}}, \tag{65}$$

we obtain from equation (65)

$$r^2 - a^2 = s_0 r . \tag{66}$$

Solving equation (66) gives

$$r = \frac{s_0 \pm \sqrt{s_0^2 + 4a^2}}{2}. \tag{67}$$

Rejecting s_0 $(-\sqrt{s_0^2 + 4a^2})/2$ since it is negative, we have as a positive value of r for which $\psi(r)$ has minimum

$$\bar{r} = \frac{s_0 + \sqrt{s_0^2 + 4a^2}}{2}. \tag{68}$$

From Figure 4 and inequality (60) we see that if

$$\frac{a(\gamma_{ms} - \gamma_{cs})}{\gamma_{cm}} > \psi(\bar{r}) , \tag{69}$$

and if r lies between the two largest positive roots of the equation

$$\frac{a(\gamma_{ms} - \gamma_{cs})}{\gamma_{cm}} = \psi(r) , \tag{70}$$

then elongation is possible; the value of r decreases until it equals the smaller of the positive solutions of equation (70). This value will exceed a. However, if $r > a$ does not lie within this range, contraction will occur.

On the other hand, if

$$\frac{a(\gamma_{ms} - \gamma_{cs})}{\gamma_{cm}} < \psi(\bar{r}) , \tag{71}$$

then inequality (60) cannot hold for any $r > a$ and hence contraction rather than elongation will occur.

Combining equations (15), (43), (45), and (58), we obtain

$$\frac{dz}{dt} = \frac{2\pi a}{3\eta V}(\gamma_{ms} - \gamma_{cs})z^2 - \frac{2\pi\gamma_{cm}}{3\eta V} \times \left(\sqrt{\frac{V}{\pi z} + a^2} - \frac{V}{2\pi z \sqrt{a^2 + \frac{V}{\pi z}}} \right) z^2 - \frac{2\pi a f_0 z^3}{3\eta V}. \tag{72}$$

Integration of equation (72) would give z as a function of t, however, the integration itself is a difficult task and for purposes of testing the theory, equation (72) might perhaps prove more convenient than its integral.

In all of these cases, we have failed to find an expression for dz/dt giving this derivative a constant value. The results of experimental work indicate that dz/dt is approximately constant at least through part of the total range of z. It is quite possible that other kinds of cell substrate interfaces exist in cultures where these cells grow. A type of interface between cell and substrate in which contact between cell and substrate occurs only near the tip of the cell-process has been described. Furthermore, frictional forces may be of a different nature than those discussed here. The variability of the volume of the filopod may also play a role. Later theoretical investigations of this problem should be concerned with these equations.

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SOME REMARKS ON THE BOOLEAN ALGEBRA OF NERVOUS NETS IN MATHEMATICAL BIOPHYSICS

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Recent demonstration by the author has shown that the fundamental equations of the mathematical biophysics of the central nervous system can be considered as describing the behavior of very large numbers of neurons, of which each one follows discontinuous laws, such as discussed by W. S. McCulloch and W. Pitts. In that light some of the old problems are discussed. The comparative merits of the "microscopic" and "macroscopic" approaches are discussed for the problem of the point to point correspondence between the retina and the cortex, with the number of connecting fibers much less than the number of cells. Some aspects of discrimination of intensities are also discussed. Finally, a few generalizations of the McCulloch-Pitts treatment are suggested, and a nervous network is constructed which illustrates some aspects of the perception of numbers.

In a previous paper (Rashevsky, 1945) we have shown that the usual equations of the mathematical biophysics of the central nervous system can be interpreted as a statistical macroscopic result of the interaction of a very large number of neurons, each following the laws now accepted as empirically established in neurophysiology. The "macroscopic" and the "microscopic" laws will from now on have to be used together, the former in those cases where a very large number of neurons is involved, the latter for relatively small numbers. It is the purpose of this paper to consider briefly some problems which may involve the "microscopic" laws, for the description of which Boolean algebra is the adequate analytical tool (McCulloch and Pitts, 1943; Householder and Landahl, 1945).

I

The problem of a point to point correspondence between the retina and some region of the occipital lobes has been treated from the "macroscopic" point of view by H. D. Landahl (1939). It does not seem to be possible on this basis to account for the fact that in certain parts the number of optical fibers is about one hundred times less than the number of cells which they connect. W. S. McCulloch (unpublished) has shown that by considering rather general temporal patterns of discharge in a fiber, it is possible to construct a "microscopic" mechanism which will give the desired effect. It is interest-

ing to consider as temporal patterns simple periodic discharges with different periods.

Assuming with W. S. McCulloch and W. Pitts (1943) that all synaptic delays are approximately constant, being equal to about 0.5 ms, and denoting this constant by δ, it is readily seen that a circuit as shown in Figure 1a will respond only when fiber I fires regularly

FIGURE 1

with a frequency $1/\delta$. Except where otherwise indicated, we symbolically assume (McCulloch and Pitts, 1943) that a simultaneous excitation of two terminal bulbs is necessary to make a neuron fire. Inhibitory synapses are symbolized by loops and we consider here only absolute inhibition. The circuit of Figure 1b will respond to a frequency $1/2\delta$. By interculating n internuncials, we obtain a circuit which responds to a frequency of $1/n\delta$.

Hence, if a fiber discharges simultaneously with a large number of frequencies, all of the form $1/n\delta$, where n is a positive integer, and if this fiber branches off collaterals, each to a proper circuit, each circuit will respond if, and only if, a corresponding frequency is present in the discharge of the fiber.

Inasmuch as the usually observed steady frequencies in optic fibers are of the order of 20 per second or below, n must be no less than 100. If we wish the fiber to carry 100 frequencies of the form $\nu = 1/n\delta$, then the highest one will be $\nu_{max} = 1/100\delta = 20$ sec^{-1}, while the lowest will be $\nu_{min} = 1/200\delta = 10$ sec^{-1}. There would be no difficulty in having one fiber per 100 retinal cells. A difficulty appears, however, in the necessity to assume that each retina cell connected to the fiber fires with a frequency $1/n\delta$, n being an integer, for if n is not an integer, no mechanism of the type shown in Figure 1 will respond to it. In fact, *no* circuit based on the assumption of a constant δ will do that.

Inasmuch as the retinal cells are seats of rather complex photochemical reactions, the possibility is open that the nature of the peripheral photosensitive processes provides for each cell a frequency of discharge of the form $\nu = 1/n\delta$. But at present this must be an explicit additional assumption.

II

The mechanism for discrimination of intensities suggested by N. Rashevsky (1938b, 1940) and developed in detail by A. S. Householder (1939, 1940a, b; Householder and Landahl, 1945) is based on

the macroscopic concept. Using, however, at the afferent end of a slowly adapting fiber such circuits as shown in Figure 1, it is seen that a stimulus of a given intensity S which results in a steady frequency $\nu(S)$ may be relayed to different parts of the brain depending on its intensity. Empirically it is known that approximately

$$\nu = \log S . \tag{1}$$

But only frequencies of the form $1/n\delta$ will produce a response at all. In order to have a mechanism that will account for perception of a continuous range of frequencies, we must consider the period of latent addition τ, and thus obtain

$$\nu = \frac{1}{n(\delta \pm \tau)}, \tag{2}$$

with $\tau < \delta$. The smallest discriminable difference of frequencies is

$$\delta\nu = \frac{1}{\delta \pm \tau}\left(\frac{1}{n} - \frac{1}{n+1}\right) = \frac{1}{\delta \pm \tau}\frac{1}{n(n+1)}. \tag{3}$$

For frequencies of the order of 200 sec^{-1} or less, $n > 10$, and instead of equation (31), we have approximately

$$\delta\nu = \frac{1}{\delta \pm \tau}\frac{1}{n^2}. \tag{4}$$

From equations (1), (2), and (3) it follows that

$$\frac{\delta S}{S} = (\delta \pm \tau)\log^2 s, \tag{5}$$

which is contrary to experience. The old "macroscopic" theory (Householder and Landahl, 1945) is better in this case, although further modifications of the "microscopic" model may lead to different results.

We may consider a group of rapidly adapting fibers so that the frequency in each fiber is independent of the intensity S of the stimulus. Let, however, due to differences in thresholds, the number of excited fibers increase with S. The circuit shown on Figure 2 pro-

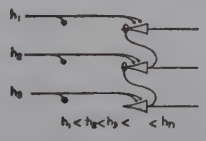

FIGURE 2

vides for an excitation of a different second order neuron for sufficiently different values of S. But the relation between S and the J.N.D. δS is now determined solely by the distribution function of the thresholds h_i, which must be chosen so as to give a correct relation between δS and S.

A distribution function of thresholds enters also into the "macroscopic" theory of discrimination. All the work of A. S. Householder (1939, 1940a, b; Householder and Landahl, 1945) indicates, however, that the gross results of the theory do not depend on the exact form of that distribution function as they would in the present case.

III

We shall now discuss a mechanism for the discrimination of several temporally separated stimuli affecting the same end organ. On a "macroscopic" scale a somewhat similar problem has been discussed by H. D. Landahl (1940).

In the following, whenever logical symbolism is introduced, we shall, for typographical convenience, use the notations of D. Hilbert and W. Ackermann (1928) with the following two modifications: we shall use for equivalence the symbol "$\equiv$" instead of "$\sim$", and for conjunction a dot instead of "&".

The application of Boolean algebra to the theory of nervous nets is based on the circumstance that simple neuronic structures correspond to the functor S (McCulloch and Pitts, 1943), disjunction, conjunction, and negation, as illustrated by Figures 1a-1d of W. S. McCulloch and W. Pitts, (1943). Just as any complex propositional function is built up by means of those four fundamental operators, so is any complex network built of the above-mentioned fundamental units. We shall introduce two new structures corresponding to the unlimited existential operator $(Ex)\ N(x)$ meaning "there is an x for which $N(x)$ holds" and the limited existential operator $(Ex)_k N(x)$ meaning "there is an x amongst the integers from 0 to k for which $N(x)$ holds." That the structure corresponding to (Ex) is a closed circuit has been incidentally mentioned by W. S. McCulloch and W. Pitts (1943, p. 131, last line). Their illustration (1i) contains, however, a slip, in that the circle consists of a single neuron. This could not be the case in the microscopic picture (Rashevsky, 1945), where at least two neurons are necessary.

Using δ as the unit of time, we find the following:

To the analytical expression

$$N_2(t) \equiv (Ex)\ N_1(t-x-1), \tag{6}$$

where x is an integer including zero, corresponds the circuit shown

in Figure 3a. To the expression

$$N_2(t) \equiv (Ex)\ k\, N_1(t-x-1), \tag{7}$$

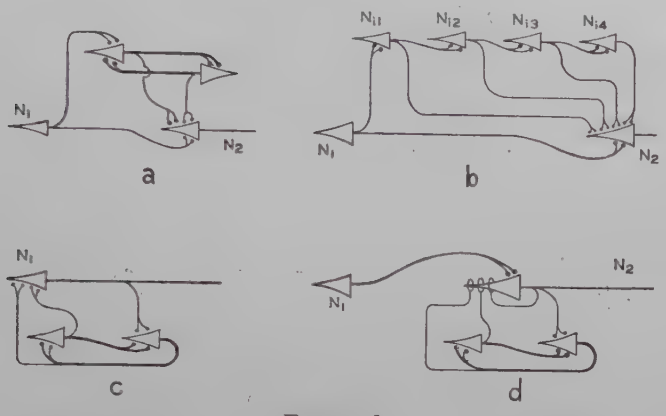

FIGURE 3

corresponds the circuit of Figure 3b, with k neurons N_{ij}.

A circuit, shown in Figure 3c, corresponds to

$$N_1(t) \equiv (Ex)\ N_1(t-x-2), \tag{8}$$

and to the expression

$$N_2(t) \equiv N_1(t-1) \cdot (\overline{Ex})\ N_2(t-x-1) \tag{9}$$

corresponds the circuit of Figure 3d.

We now proceed to construct a network consisting of a single afferent N_0, and of m efferents N_1, $N_2 \cdots N_m$, and having the following properties: Let N_0 fire at any irregular intervals, *provided that all those intervals are integer multiples of* δ, then when N_0 fires for the first time, N_1, and only N_1, responds; when it fires for the second time N_2, and only N_2, responds; when it fires for the j-th time N_j, and only N_j responds. Analytically this is expressed by

$$N_j(t) \equiv N_0(t-1) \cdot (Ex)\ N_1(t-x-1) \cdot (Ex)\ N_2(t-x-1) \cdots$$
$$\cdots (Ex) N_{j-1}(t-x-1)\ (\overline{Ex})\ N_j(t-x-1).$$

But this is equivalent to the requirement

$$N_j(t) \equiv N_0(t-1) \cdot (Ex)\ N_{j-1}(t-x-1). \tag{10}$$

The corresponding circuits are shown in Figure 4. The neuron N_1 is assumed to have a threshold of 4, while the neurons of the reverberating circuits and all other neurons N_j have thresholds 2.

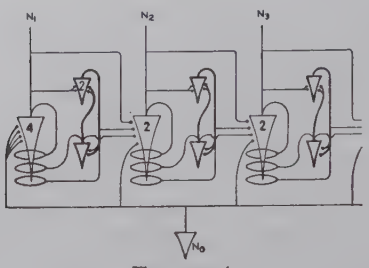

FIGURE 4

If thus the same stimulus is applied to N_0 several times in succession, each application elicits the response of a different N_j. The activity of a given N_j may release a set of motor reactions, verbal or otherwise, which will be different for each repetition of the same stimulus. We have here an elementary process of counting.

If instead of the unlimited existential operator we use in expression (10) the limited existential operator, a circuit is obtained similar to that of Figure 4, but in which instead of circles, structures shown in Figure 3b are used. Such a circuit will have the property that repetitions of the same stimulus will be "counted" only when the intervals between the individual repetitions do not exceed a certain value determined by the value of k in $(Ex)k$. Speaking antropopsychically, we may say that in this case we "forget" the preceding repetitions if the intervals become too large. This, perhaps, may correspond to actual situations.

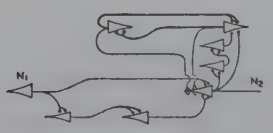

FIGURE 5

Consider now the circuit shown in Figure 5. Denoting by $N(t, t+2)$ the statement that neuron N fires at the moments t and $t+2$, the analytical expression for the circuit of Figure 5 is

$$N_2(t, t+2) \equiv N_1(t-1) \cdot (\overline{Ex})\,[N_2(t-x-2) \cdot N_2(t-x)]. \tag{11}$$

In words: a single firing of N_1 results in a succession of two firings of N_2, provided N_2 has not fired in such a way before. We may now construct a circuit corresponding to

$$N_j(t, t+2) \equiv N_0(t-1) \cdot (Ex)\, N_1(t-x-3, t-x-1) \cdot (Ex)\, N_2(t-x-3, t-x-1) \cdots (Ex)\, N_{j-1}(t-x-3, t-x-1) \cdot (\overline{Ex})\, N_j(t-x-2, t-x-1). \tag{12}$$

Returning again to one afferent N_0 and n efferents N_j, we may conceive that N_0 is connected with each N_j both by means of a circuit 3d, which is the fundamental unit used in constructing the circuit of Figure 4, and by means of circuits of Figure 5. In other words, we now construct a circuit which corresponds to both expressions (10) and (12). The circuit corresponding to expression (12) may, however, be inhibited by a permanently excited closed circuit C_1 which itself is inhibited by the single excitation of the n-th efferent N_n. At the same time let the excitation of N_n excite another closed circuit C_2, which inhibits all circuits of the type of Figure 3a, at all the N_j's. Then up to n repetitions we shall have the situation described for Figure 4. But for the $(n+1)$st repetition of the stimulus, N_1 will fire twice, for the $(n+2)$nd repetition —N_2 will fire twice, and so forth. Putting

$$(E_1x)\, N_i(t-x) = [(Ex)\, N_i(t-x)] \cdot [(\overline{Ey})\, N_i(t-y)] \cdot [x \neq y], \tag{13}$$

we have analytically

$$N_j(t) \equiv N_0(t-1) \left[\sum_{i=1}^{i=j-1} (Ex)\, N_i(t-x-1) \right] \cdot [(\overline{Ex}) N_j(t-x-1)] \cdot [j < n];$$

$$N_j(t, t+2) \equiv N_0(t-1) \cdot \left[\sum_{i=1}^{i=j-1} (Ex)\, N_i(t-x-3, t-x-1) \right] \cdot [(\overline{Ex})\, N_j(t-x-3, t-x-1)] \cdot [(E_1x)\, N_n(t-x-3(j-1)]. \tag{14}$$

The circuit becomes too complicated to permit a practically useful drawing.

The great disadvantage of the above mechanism is the requirement that all stimuli at N_0 be repeated at intervals which are integer multiples of δ, at least with an error not exceeding the period of latent addition. If this is not the case, the mechanism breaks down.

The situation may be remedied in two ways. First, we may introduce some mechanism between N_0 and the rest of the system which

will provide for such a regulation of the intervals, even for stimuli spaced differently in time. Second, we may construct a circuit similar to the one represented in Figure 4, in which, however, pathways are substituted for fibers. In other words, we may consider a similar mechanism on a "macroscopic" scale. The circuit then is considerably simplified since, due to the continuous excitation of the pathways, each neuron group N_i needs to connect with only one pathway from each preceding N_{i-1} (Figure 6). The group of neurons N_0 must be of a

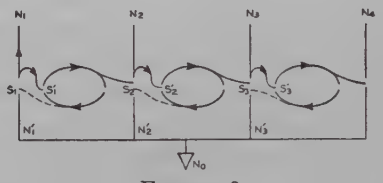

FIGURE 6

mixed excitatory type (Rashevsky, 1938, 1940; Householder and Landahl, 1945) characterized by

$$A > B, \quad a > b; \quad \frac{A}{a} < \frac{B}{b}. \tag{15}$$

For otherwise, a continuous stimulus to N_0 will produce a successive series of responses N_1, N_2, N_3, etc. Moreover, the duration of excitation of N_0 for a continuous stimulus must be less than the delays at the connections s_j and s_j' (Figure 6). Also, the saturation value E_0 of N_0 must be reached for very small values of the intensity S of the stimulus applied to N_0 so that the intensities E_i' of excitation of all the N_i' are independent of the intensity of the stimulus at N_0. If, for simplicity, we assume that the constants of all the pathways converging on any connection s_i are the same, and if we denote by E_i'' the intensity of excitation of each of those pathways, while E_i denotes the intensity of excitation of the inhibiting pathways, then we must have

$$\frac{AE_i'}{a} - \frac{BE_i}{b} < h_i < \frac{AE_i'}{a} + \frac{AE_i''}{a} - \frac{BE_i}{b}. \tag{16}$$

With all the above requirements satisfied, the "macroscopic" network shown in Figure 6 will possess the necessary property. Various quantitative aspects may be studied by applying the fundamental equations of the mathematical biophysics of the central nervous system.

It seems somewhat awkward to have to construct by means of Boolean algebra first a "microscopic circuit" and then obtain a simpler one by a transition to the "macroscopic" picture. We should expect that a generalization of the application of Boolean algebra should be possible so as to permit its use for the construction of networks in which time relations are of a continuous, rather than of a quantized, nature.

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BULLETIN OF
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SOME QUANTITATIVE ASPECTS OF SHOCK THERAPY IN PSYCHOSES

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A quantitative analysis of the immediate results of insulin and electric shock therapy given a series of patients with schizophrenic reactions leads to a definition of minimum standards of adequacy of treatment and suggests that the immediate outcome in adequately treated patients depends on the duration of the illness. The experimental results are rationalized by a formal theory which postulates a slow development of the illness, improvement to some extent after each treatment, and a slow relapse.

Although a large number of papers on the results of shock therapy have appeared since 1936, little quantitative is known about it. It is to be expected *a priori* that the results of treatments will depend on the number of shocks administered, as well as on the previous duration of the illness. The purpose of this paper is to make a step towards the study of the percentage P of recovery as a function of the number n of shocks and the duration τ of the disease in months. Because of the small number of cases analysed, our results cannot claim anything more than a general indication of the type of existing relations.

A preliminary analysis has been made of the results in 170 courses of electric shock therapy and 185 courses of insulin shock therapy given in schizophrenic reactions at the Milwaukee County Hospital for Mental Diseases. The results were determined as of two to four weeks after the completion of therapy.

Duration. The duration of the illness before treatment was determined from the history taken on admission. Where an estimate was given, as for example, six to eight months, the midpoint was taken as the time of onset.

If a patient was discharged as recovered, then was readmitted and given shock therapy, the onset of illness was considered to be between the two admissions. If he had been discharged only as improved, he was assumed not to have recovered in the interval between admissions unless a very definite history to the contrary was ob-

tained; his illness was thus assumed to have begun before the first admission and to have continued until the time of treatment.

Number of treatments. The number of treatments in the insulin group was defined as the number of days on which the patient became unconscious during the treatment; that is, only one coma could be experienced per insulin day. No distinction was made between long or short, deep or shallow comas. If no coma was produced, the patient was excluded from the series. The occurrence of a spontaneous convulsion during the insulin day was not counted as an extra treatment. None of the patients received metrazol or electric shock therapy in conjunction with their insulin.

The number of electric shock treatments was defined as the number of times a current was passed through the patient, whether or not it produced a grand mal seizure.

Insulin treatments ordinarily were given five times per week and electric shock treatments twice per week. Slight disturbances of this rhythm was disregarded in this study. A course was counted as terminated if more than thirteen days elapsed without treatment. All the cases discussed here received adequate treatment defined as having not less than thirty electric shock treatments, or not less than fifty insulin comas. Values for n greater than these limits are thus somewhat arbitrary.

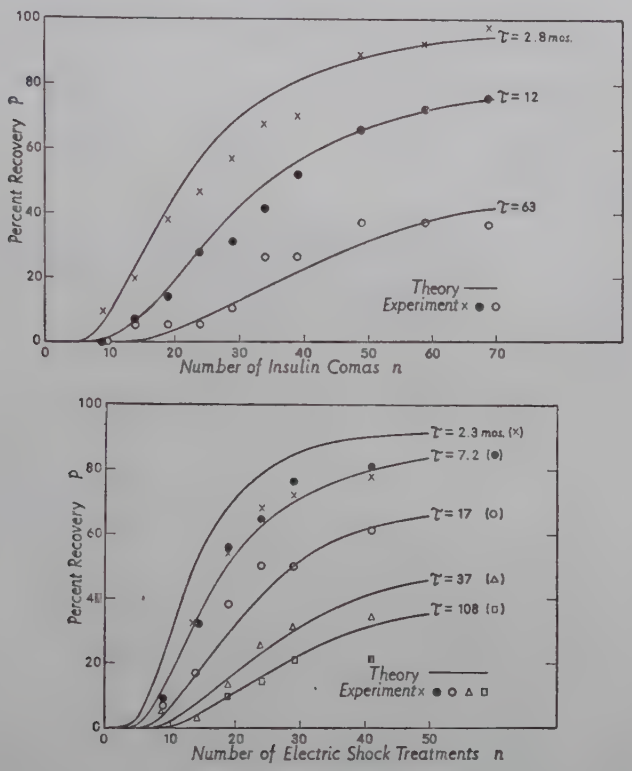
Criteria of improvement. The degree of improvement was judged by the progress note written shortly after the termination of treatment. Recovery was taken to mean that the patient was free of symptoms and able to return to his former place in society. All lesser degrees of improvement were counted, in this study, as failures.

Diagnosis. The diagnosis in all cases was schizophrenia.

Sex. All the insulin patients were women. Both sexes were represented in the electric shock group. Because in the large series of J. B. Ross and B. Malzberg (1939; Malzberg, 1943) there is shown no significant difference in the results of shock therapy in the two sexes, the electric shock results in this study were not shown according to sex, and the absence of men in the insulin group is not regarded as important.

Results. In the total insulin group, 45% of the courses of treatment resulted in recovery; in the electric shock group the percentage of success was 41. The over-all results in the present series are of the same order of magnitude as those usually reported from other hospitals. It is therefore possible that the breakdown of the figures, which shows some interesting correlations, applies equally well to the reports from other institutions. For the adequate groups the corresponding percentages are 76 and 59.

The results are shown graphically in Figures 1 and 2 for the cases which received adequate treatment. As said above, the small number of cases does not permit many conclusions. The general result, however, seems to indicate that the function $P(n, \tau)$ increases with n, reaching an asymptotic value approximately at $n = 30$, and



FIGURES 1 AND 2

that this asymptotic value is a decreasing function of τ. The individuals having durations falling into arbitrary intervals were grouped, and to this group the mean duration τ has been assigned. The intervals especially in the insulin data are large because the number of cases is small. The number of cases in each group was as follows: for the insulin data from $\tau = 2.8$ to $\tau = 63$ the numbers are 37, 29, and 19, and for the electric shock data from short to long duration the numbers are 57, 34, 18, 32, and 29.

Theoretical considerations. We shall make the following definitions:

$S =$ a measure of the state of the individual

$H = S$ for average "normal" individual
δ = decrement from average normal required to notice onset of abnormality
Δ = decrement from average normal required to make diagnosis of return to normality ($\Delta < \delta$)
m = number of shock treatments, equally spaced in time and of equal intensity—first treatment origin of time scale
n = value of m for which cure ($S = H - \Delta$) takes place
τ = duration of disease at initiation of therapy, time since $S = H - \delta$.

Under normal circumstances one may assume that various events may act to change S, but that homeostatic mechanisms influence the outcome. If $Q(S, t)$, which may depend upon past events implicitly, is a measure of the effect of these events, S may be governed by a relation of the form

$$\frac{dS}{dt} = Q(S, t) - \alpha(S - H)\, f(S), \tag{1}$$

so that the normal value of S returns spontaneously toward H if the term Q does not exert too large an influence. If the effect of nonlinearity of the homeostatic mechanism can be summarized by setting $f(S) \equiv (S - h)S$, then equation (1) becomes

$$\frac{dS}{dt} = Q(S, t) - \alpha(S - H)(S - h)S. \tag{2}$$

For $Q = 0$, H, h, and 0 are equilibrium values of S, H and 0 being stable, h being unstable. Suppose now that S is in the neighborhood of H and that Q becomes large negatively and remains so for a long enough period of time. Then, according to equation (2), S will decrease toward zero even after Q ceases to be negative, unless Q is too large positively. Consider only the case in which the average value of Q is negligible so that we may set $Q = 0$. Then roughly, for $S < h$, S decays exponentially according to

$$S = (H - \delta)\, e^{-b(t+\tau)}, \tag{3}$$

where $b = \alpha H h$, and $S = H - \delta$ for $t = -\tau$. This states that the condition of the individual spontaneously recedes from the normal, being, by definition, just noticeably abnormal ($H - \delta$) at $t = -\tau$, τ being the duration, and the time being measured from initiation of treatment.

The effect of the shock treatment is evidently to raise S eventually. The data suggest that for the first few trials S may not be increased, but for the present we shall pass over this. In terms of equation (2), this means that the treatment is equivalent to a positive Q over a period of time. Furthermore, S cannot continue to rise indefinitely so that the rate of rise of S with n must decrease for large n. This would occur if in addition to the terms on the right hand side of equation (2) there are terms which make for more rapid adjustment, but toward the value of S at some previous time, i.e., of the form $-\beta S(t-\tau')$.

If t_1 is the constant time between treatments, then $m = t/t_1$ may be introduced as the variable. Furthermore, if the period of treatment is not too long so that S from equation (3) will not have been greatly altered, then for this period we will have

$$\frac{dS}{dm} = aK - aS(t-\tau'), \tag{4}$$

where aK/t_1 is the effective Q due to treatment and $a = \beta t_1$. If τ' is larger than the period of treatment but too much so, then $S(t-\tau') = S_\tau$ from equation (3) with t set equal to zero, being approximately a constant. Hence from equations (3) and (4), $(t << \tau)$,

$$S = (h-\delta)e^{-b\tau} + K(1-e^{-an}). \tag{5}$$

If $m = n$ for which cure occurs, then

$$H - \Delta = (H-\delta)e^{-b\tau} + K(1-e^{-an}), \tag{6}$$

or if $k = K/(H-\delta)$, and $\varepsilon = (\delta - \Delta)/(H-\delta) < 1$, equation (6) becomes

$$1 - e^{-b\tau} + \varepsilon = k(1-e^{-an}). \tag{7}$$

Now k measures the relative effectiveness of the treatment to any individual. It is reasonable to expect that the logarithm of k is distributed normally over the population. If $p(z)$ is the normal curve for deviating z then we may write $p\left(\frac{1}{\sigma}\log k/\bar{k}\right)$, where σ is the standard deviation and $\bar{k}$ is the median value of the k's in the population. From equation (7) we may then write for the per cent cured for those individuals with duration τ and having had m treatments, the relation

$$P(n,\tau) = \int_{1/\sigma \log k/\bar{k}}^{\infty} p(z)\,dz, \tag{8}$$

with k being given by equation (7). The curves in Figures 1 and 2 illustrate the form of equation (8).

If, on the average, $H - \Delta < h$, then more cases will relapse than remain cured since these will tend again toward the lower equilibrium. This will depend upon the value of Q which is generally unknown. Given the distribution of the h's relative to $H - \Delta$, and, disregarding the effect of Q, one can compute the percentage of relapses. At first glance this does not depend upon τ, but this is because we have not really taken into account the term $\beta S(t - \bar{\tau})$. Additional treatments after apparent cure would be beneficial according to this picture, especially so for short durations.

In Figures 1 and 2 are shown curves computed from equations (8) and (7) in which $\sigma = .41$, $b = .045$, $\varepsilon = .67$ for both sets of data, $\bar{k} = 1.57$ and 1.69, $a = .05$ and .03 for the electric and insulin shock data respectively. If we take $\Delta = 0$, and set $H = 1$, i.e., use arbitrary units with the normal level unity, then $\delta = .40$, $K = 1.94$ and 1.01. The effectiveness per treatment, aK, is .047 and .030 in the two cases. From the point of view of the present theory σ, b, and ε should be the same for both treatments (or any other) for equivalent groups since they are properties of the population.

In the case of the insulin data the agreement with theory is not too unsatisfactory. It should be emphasized that the numbers involved are not large, while too large a range of values of τ have had to be grouped together. In the case of the electric shock data, the agreement is less satisfactory. The principle deviation is for the short duration where the theory requires an appreciable difference between two and seven months' duration, whereas none appears. However, an appreciable difference could exist without showing up because the numbers involved are not large enough.

The data for large τ seem to reach an asymptotic value too soon to be accounted for by the theory. However, as pointed out above, the data for large n are particularly unreliable. But undoubtedly further modification of the theory will be required when additional data are available.

Since the parameters are closely interconnected, the values given above are to be considered as very rough approximations. Furthermore, the removal of simplifying approximations may change the shape of the curves somewhat while the values of the parameters may be changed considerably.

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BULLETIN OF
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A NOTE ON THE MATHEMATICAL BIOPHYSICS OF CENTRAL EXCITATION AND INHIBITION

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Some relations between the temporally macroscopic theory of central excitation and inhibition and the temporally microscopic theory of nervous nets are suggested.

Consider a neuron c_n which is acted upon by excitatory neurons, $c_1, \cdots, c_e, \cdots, c_p$ and inhibitory neurons $c_{p+1}, \cdots, c_j, \cdots, c_{p+q}$. Let θ be the least number of excitatory neurons, firing within a time δ, required to fire c_n. The average frequency ν_n with which c_n fires will be given by [Householder and Landahl, 1945, chap. xv, equation (3)]

$$\nu_n = \delta^{\theta-1}(1 - \delta \sum \nu_j)\,({}^p\nu^\theta), \tag{1}$$

where terms of degree greater than θ have been neglected and where $({}^p\nu^\theta)$ is the sum of all possible terms of degree θ in ν of the p different ν_e's taken θ at a time.

If $p < \theta$, c_n cannot fire. If $p = \theta$, then ν_n is proportional to the product of the ν's. If $p = \theta + 1$, there are p terms of degree θ. In this case, doubling any ν practically doubles ν_n.

If the ν's are not of too different magnitude, one may write very roughly

$$\nu_n = \delta^{\theta-1}(1 - \delta \sum \nu_j)\,\frac{p!\,\nu^\theta}{(p-\theta)!\theta!}, \tag{2}$$

where $\bar{\nu}$ is some average value of the ν's, frequently between the arithmetic and geometric means. This can also be written approximately as

$$\nu_n = \frac{(\delta\bar{\nu})^{\theta-1}(p-1)!\sum \nu_e}{(p-\theta)!\theta!} - \frac{\delta^{\theta-1}\nu^\theta\, p!}{(p-\theta)!\theta!}\sum \nu_j, \tag{3}$$

generally a better approximation than equation (2) if $\bar{\nu}$ is the geometric mean and if $p > \theta + 1$.

The quantity ν_n can be considered as the stationary state frequency of c_n and should thus be proportional to the quantity E of N.

Rashevsky's theory (Rashevsky, 1938). But then E is linear with the E's of the afferent fibers. Thus ν_n should be linear in ν_e (excitatory) and ν_j (inhibitory), whereas the first term on the right hand side of equation (3) contains $\bar{\nu}^{\theta-1}$.

For the particular case in which only a subgroup m of the p fibers vary in magnitude, the others remaining constant in their activity, the effect of the coefficient $\bar{\nu}^{\theta-1}$ is reduced. In particular, if $p - m = \theta - 1$, ν_n is given by

$$\nu_n = \delta^{\theta-1} \nu_1 \nu_2 \cdots \nu_{p-m} \sum_{i=1}^{m} \nu_i - m \delta^{\theta-1} \bar{\nu}^{\theta} \sum \nu_j . \tag{4}$$

Thus for the case of several equivalent afferents acting upon a single neuron, approximate correspondence occurs for rather restricted conditions.

We shall consider next some temporal relationships. If the frequency ν_n determined from equation (2) depends upon time, due to variations in ν_e and ν_j, so that ν_{ns} is the frequency at time $s\delta$, then the probability that c_n fires for the first time in the interval 0 to t is given by

$$P(t) = \sum_{s=1}^{s=t\cdot\delta} \prod_{r=1}^{r=s-1} (1 - \delta\nu_{nr}) \delta\nu_{ns} . \tag{5}$$

For constant ν_n, we have

$$P(t) = 1 - (1 - \nu_n\delta)^{t/\delta} . \tag{6}$$

For $\delta\nu_n << 1$, the above equation reduces to

$$P(t) = 1 - e^{-\nu_n t} . \tag{7}$$

This suggests a possible identification of $P(t)$ with the excitatory factor. If we set $P(t) = 1/2$ (or some arbitrary value), we can determine the value t_n of t for which the probability is one-half that the first firing occurs prior to that time, so that t_m is the median reaction time given by

$$t_m = \frac{\log 2}{\nu_n} . \tag{8}$$

From the two-factor theory, the time to reaction will be given by the solution of a complex equation. If AE/a for each excitatory afferent is large compared with the threshold h_n and a similar inequality holds for the inhibitory neurons, then one may write approximately

$$t'_m = \frac{h_n}{\Sigma A_e E_e - \Sigma B_j E_j} \tag{9}$$

for the median reaction time.

But if ν_n can be approximated by equation (4), the similarity between equations (8) and (9) is evident since $E_e \propto \nu_e$ and $E_j \propto \nu_j$. However, the latter expression involves a linear combination, the former involves the sum.

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BULLETIN OF
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A SUGGESTION FOR ANOTHER STATISTICAL INTERPRETATION OF THE FUNDAMENTAL EQUATIONS OF THE MATHEMATICAL BIOPHYSICS OF THE CENTRAL NERVOUS SYSTEM

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In a preceding paper an interpretation of the ε and j factors has been given in terms of an average effect of a large number of interneurons. In the present paper, a different interpretation is given in terms of the probability of a sufficient number of afferents to fire within the period of latent addition of the efferent. From this interpretation it follows that the old equations for ε and j are only first linear approximations to more complicated equations, the nature of which is suggested by this interpretation.

In a previous paper (Rashevsky, 1945) we suggested a statistical interpretation of the ε and j factors. These were considered as measuring the number of self-circuited interneurons. The "synapse" of the mathematical biophysicist thus becomes a rather complicated structure, involving a very large number of interneurons.

In the present note we outline a different approach to the problem.

Consider an efferent neuron whose threshold in terms of the minimum number of terminal bulbs which must be excited is n_1. Let N afferent fibers synapse with this neuron, and consider for simplicity that they all have only one terminal bulb each on the neuron. Let $n_1 < N$. Let the average frequency ν of discharge be the same in all afferents. Let δ be the period of latent addition.

The probability for any one impulse to arrive at the neuron within a given interval δ is equal to $\delta\nu$. The probability for n given fibers to bring impulses to the terminal bulbs within the interval is $(\delta\nu)^n$. The probability $P(n)$ for *any* n fibers to bring their impulses to the efferent neuron within the interval δ is

$$P(n) = (\delta\nu)^n \frac{N!}{(N-n)!n!}. \tag{1}$$

The smaller $P(n)$, the longer we shall have to wait for such an event to happen. If the firing of the group of afferents begins at

$t = 0$, then the probable time t_p of waiting is equal to δ for $P(n) = 1$ and to ∞ for $P(n) = 0$. Hence, we may put approximately

$$t_p = \frac{\delta}{P(n)}. \tag{2}$$

Instead of N afferents, we may consider only one afferent, which connects with the efferent through N internuncials, so that the efferent is bombarded by irregular valleys of *average* frequency ν.

Put

$$\frac{dP(n)}{dn} = -f(n). \tag{3}$$

Equation (2) gives

$$P(n) = \frac{\delta}{t_p}; \qquad dP(n) = -\frac{\delta}{t_p^2}\, dt_p. \tag{4}$$

Hence, from equations (3) and (4),

$$\frac{\delta}{t_p^2}\frac{dt_p}{dn} = f(n). \tag{5}$$

But from equation (4)

$$t_p^2 = \frac{\delta^2}{P^2(n)}, \tag{6}$$

hence

$$\frac{P^2(n)}{\delta}\frac{dt_p}{dn} = f(n), \tag{7}$$

or, if we consider the number of simultaneously excited terminal bulbs as a function of the probable time t_p, we have

$$\frac{dn}{dt_p} = \frac{P^2(n)}{\delta f(n)}. \tag{8}$$

The function $P(n)$ and hence also $P^2(n)$ is finite for $n = 0$, and is zero for $n = N + 1$, being positive in that interval. The function $f(n)$ is finite everywhere, provided $(\delta\nu)$ is sufficiently small and N not too large, so that $P(n)$ is monotonically decreasing with n. Therefore, in this case, the function

$$F(n) = \frac{P^2(n)}{\delta f(n)} \tag{9}$$

is a positive monotonically decreasing function in the interval $(0, N+1)$.

As a first *linear* approximation we may put

$$F(n) = A_1 - an. \tag{10}$$

Since the value $N + 1 = A_1/a$, at which $F(n)$ becomes zero, increases with N, we have *approximately*, with $A_1 = A_2N$,

$$F(n) = A_2N - an, \tag{11}$$

or, since $N + 1 \propto E$, the total afferent excitation, (Rashevsky, 1945) therefore

$$F(n) = AE - an, \tag{12}$$

and hence, from equation (8),

$$\frac{dn}{dt_p} = AE - an. \tag{13}$$

Equation (13) is formally identical with the equations for ε and j. Thus ε is interpreted as the probable number of terminal bulbs excited within the period of latent addition. The longer t_p, the larger this probable number, but it never can exceed N. Hence if $n_1 > N$, then no matter how long we wait, the efferent neuron will never fire. This is the equivalent of the old requirement that $h < AE/a$, since n_1 plays the role of h, and $N \propto AE/a$.

Similarly, if we consider relative inhibition (McCulloch and Pitts, 1943), j may be interpreted as the probable number of inhibitory synapses excited within the period of latent addition.

According to this interpretation, equation (13) is only a very rough approximation to the exact equation (8). The study of the latter thus leads us to a *generalization* of the present theory of central excitation and inhibition.

The time t_p at which n becomes equal to n_1 is now also only an average value. The further development of this probabilistic theory will give us expressions for the fluctuations of t_p, and hence of the reaction times. There are numerous data with which such expressions may be compared.

The next important question now arises. Can we obtain, at least approximately, the relation $E_1 = \beta(\varepsilon - j - h_1)$ for the intensity of excitation E of the efferent fiber, at such times at which $n > n_1$? With the special case, which we have so far considered, namely, N afferents synapsing with *one* efferent, this does not seem to be the case. For the quantity t_p in equation (2) will also represent the average duration between two successsive events in which any n bulbs fire within the interval δ. For a time $t > t_p$ the most probable number n of bulbs firing within the interval δ will be greater than n_1, but because of the all-or-none nature of the nervous discharge, this will not produce any changes in the latter.

The picture of N afferents synapsing with only *one* efferent is,

however, rather artificial. It is much more plausible that on the efferent side we have to consider not a single fiber, but also a pathway consisting of N_1 fibers, all of different thresholds $n_{1(i)}$, and that each afferent fiber synapses with every efferent fiber.

In this case, the efferent fiber with the lowest threshold n_1 will, on the average, fire before all other fibers. This will happen when $n = n_1$, that is, at the time t_p. For $t > t_p$, n will exceed $n_1^{(1)}$, the next lowest threshold, at a moment $t_p^{(1)}$, and so forth. After an infinite time, n will have reached its maximum value N, and all efferents whose thresholds are less than N will be firing, each with an average frequency $\nu_i = 1/t_p$. As E, and hence N, increases, the number of efferent fibers with thresholds $n_1^{(i)} < N$ will also increase. Hence E_1 will increase with n, or with N. The increase will in general not be linear. The linear relation again is only a first approximation.

If N is rather large, then the expression (1) for $P(n)$ may have a maximum. In this case $f(n)$ has a root at a point n_0 in the interval $(0, N + 1)$, and therefore, $F(n) < 0$ for $n < n_0$, becomes negatively infinite at that point, then changes sign and drops to zero for $n = N + 1$. For the case of a constant N (viz. constant E) this would mean that the n, t_p curve (or ε, t curve) will begin to rise only if it is already above n_0, thus introducing a new sort of threshold. All of these possibilities indicate possible improvements in the present theory which are likely to cover a wider range of phenomena.

That the present equations for ε and j must be considered only as formal linear approximations to some more complicated equations based on physiological concepts has been pointed out previously (Rashevsky, 1940). The present paper is a step towards establishing these more exact and complicated equations.

The author is indebted to Dr. H. D. Landahl for a discussion of the paper and for critical comments.

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BULLETIN OF
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LETTER TO THE EDITOR

The Heterarchy of Values Determined by the Topology of Nervous Nets

Since you received the article on the above topic (*Bull. Math. Biophysics*, Vol. 7, No. 2), questions have arisen concerning the dependence of the anomaly on the topology of nets. It would be helpful if you could publish the following note:

Given three dromes, each of which goes over one synaptic connection which is singly insufficient to fire its subsequent neuron but which may be reinforced from one other drome, an organism which fails to respond appetitively to any one of three sensory queues singly may respond to two by what appears to be a preference for one; and three such specious choices may exhibit the circularity of the value anomaly.

Consider three dromes—A, B, and C—so connected that no one sustains activity without summation from the afferent component of one other drome and let the net be such that B (and only B) necessarily contributes to A; similarly, C (and only C) to B, and A (and only A) to C. Presented with a stimulus a, b, or c separately, there will be no response; but given any pair, a and b, or b and c, or c and a, the organism will appropriate a, b, or c, respectively; and given a, b, and c, the organism will appropriate all three. Obviously the net resembles Figure 4 of the article in question except that the threshold of the afferent neurons is now such as to require impulses from the terminations of two axons, and that the heterodromic actions are summative instead of inhibitory. The same topological considerations apply. The preference, whether or not it be a true choice, is determined by a diadrome, which is no less a diadrome because its heterodromic connections are summative instead of inhibitory.

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June 20, 1945

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BOOK REVIEW

SCOPE OF THE BULLETIN

1. The Bulletin is devoted to publications of research in Mathematical Biophysics, as contributing to the physicomathematical foundations of biology in their most general scope.

2. Papers published in the Bulletin cover physicomathematical theories as well as any other mathematical treatments of biological phenomena, with the exception of purely statistical studies.

3. Mathematical studies in physics or in borderline fields in which a direct connection with biological problems is pointed out are also accepted.

4. Emphasis is put upon the mathematical developments, but a description and discussion of experimental work falls also within the scope of the Bulletin provided that description or discussion is made in close connection with mathematical developments *contained in the same paper*.

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PREPARATION OF MANUSCRIPTS

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In writing equations, slanted lines should be used wherever possible.

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